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Vaccination and All-Cause Child Mortality From 1985 to 2011: Global Evidence From the Demographic and Health Surveys

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Based on models with calibrated parameters for infection, case fatality rates, and vaccine efficacy, basic childhood vaccinations have been estimated to be highly cost effective. We estimated the association of vaccination with mortality directly from survey data. Using 149 cross-sectional Demographic and Health Surveys, we determined the relationship between vaccination coverage and the probability of dying between birth and 5 years of age at the survey cluster level. Our data included approximately 1 million children in 68,490 clusters from 62 countries. We considered the childhood measles, bacillus Calmette-Guérin, diphtheria-pertussis-tetanus, polio, and maternal tetanus vaccinations. Using modified Poisson regression to estimate the relative risk of child mortality in each cluster, we also adjusted for selection bias that resulted from the vaccination status of dead children not being reported. Childhood vaccination, and in particular measles and tetanus vaccination, is associated with substantial reductions in childhood mortality. We estimated that children in clusters with complete vaccination coverage have a relative risk of mortality that is 0.73 (95% confidence interval: 0.68, 0.77) times that of children in a cluster with no vaccinations. Although widely used, basic vaccines still have coverage rates well below 100% in many countries, and our results emphasize the effectiveness of increasing coverage rates in order to reduce child mortality.

bacillus Calmette-Guérin; child mortality; diphtheria-pertussis-tetanus; measles; missing data; polio; tetanus; vaccinations

Abbreviations: BCG, bacillus Calmette-Guérin; DHS, Demographic and Health Survey; DPT, diphtheria-pertussis-tetanus.

There is evidence that vaccines are effective against specific diseases such as tuberculosis (1), measles (2), and tetanus (3, 4) in children. Increases in vaccine coverage have therefore been seen as an important strategy for reducing infant and child mortality rates (5). There has been a series of coordinated global efforts to increase immunization rates in developing countries as a means of achieving improvements in child health, including the Expanded Program on Immunization and the Global Alliance for Vaccines and Immunization (6). The period from 2011 to 2020 has been termed the "Decade of Vaccines" (7). The coverage of vaccinations (as measured by the proportion of children receiving 3 doses of the diphtheria-tetanus-pertussis (DPT) vaccine by 12 months of age) has increased substantially, from 5% or less in 1974 to 75% in 1990 and 84% in 2013, albeit with important regional, national, and subnational variation in achieved coverage (8, 9). Increases in coverage in Africa were achieved with a series of supplementary immunization activities in the late 1990s that were successful in reaching 24 million children between 1996 and 2000 (10).

Almost 20 million children failed to receive all 3 doses of the DPT vaccine in 2010; a third of those children were in Africa, and they were mainly concentrated in 10 countries (11). In addition, other vaccines have lower levels of coverage, with much lower rates for the measles vaccine than for the DPT vaccine. Although the number of vaccine-preventable deaths is large, the proportion of deaths caused by vaccine-preventable diseases appears to be relatively small; for example, measles accounted for 4% of all deaths in children younger than 5 years of age in the period from 2000 to 2003, and

tetanus accounted for an additional 3% (12). These figures had been reduced even further by 2008 (13). Nevertheless, studies of the cost effectiveness of vaccinations in which only the association with disease-specific mortality was used found it highly cost effective (14).

However, there is potential for routine vaccines to have an impact above and beyond the expected association with the specific disease. The introduction of the measles vaccine in some African communities in the 1980s led to a far greater reduction in overall child mortality than would be expected if it just affected mortality from measles alone (15). Similar large decreases in the incidence of all-cause mortality were found after the introduction of measles vaccination in Matlab, Bangladesh (16). There is also some evidence that the bacillus Calmette-Guérin (BCG) vaccine is protective against neonatal morality, as well as some suggestion that DPT vaccination might increase mortality in some settings (17). The hypothesis that vaccines have nonspecific effects on mortality has received validation in animal studies in which a plausible mechanism was demonstrated. Administration of the BCG vaccine in mice led to trained immunity via epigenetic reprogramming (18).

Despite recent progress in reducing the probability of dying between birth and exactly 5 years of age expressed per 1,000 live births (hereafter referred to as under-5 mortality) (19), there has been a renewed focus on implementing interventions that would allow countries to reach the target of a reduction in child mortality to two thirds of its 1990 level as set by the fourth Millennium and Development Goal. Increases in immunization might provide a highly cost-effective mechanism for further reducing child mortality rates. However, many studies on the cost effectiveness of vaccines have relied on calibration studies and simulation exercises, with measures of the association between vaccination status and mortality often taken from specific cohorts in localized areas (14, 20). There are likely to be important differences both across and within countries in terms of the effectiveness of vaccination. One issue is how vaccines are administered, a factor that could potentially affect vaccine efficacy. For example, there is substantial variation in the timing of vaccination in low- and middle-income countries (21). A second issue is that the actual effectiveness of a vaccine might be lower in practice in large-scale implementation than in small-scale studies (22) because of failures of the cold chain, storage, and handling. A third issue is that the effectiveness of vaccination in reducing child mortality may depend on other factors, for example, the socioeconomic status of the family and the child's nutrition (23), making the average effectiveness in a population different from that found in small studies.

From a policy perspective, it is important to understand whether previous findings from randomized controlled trials and observational studies based on specific cohorts can be generalized to diverse populations that experience different levels of economic development, disease environment, and health care systems (24). With some exceptions (25), there have been relatively few previous studies in which the relationship between basic childhood vaccines and all-cause mortality have been examined with population-based data in more than a limited number of countries; most studies have been based on data from a single location. The advantage of our approach is that we used nationally representative data from multiple countries that reflect a wide variety of populations and are likely to have good external validity (26). Our data contain information on all 5 basic vaccines and mortality data for children until they are 5 years of age. Our methodological contribution is that we introduced a correction for potential selection bias induced by missing data on children who died.

We collected information from a large number of developing countries using Demographic and Health Surveys (DHS) to examine the relationship between cluster-level vaccination coverage and cluster-level under-5 mortality. We focused on the associations of all-cause mortality with the BCG, DPT, polio, measles, and maternal tetanus vaccines while controlling for the cluster's socioeconomic and demographic characteristics. In the present study, our goal was to establish the relationship between mortality and immunization in population-based data. Given recent findings in the literature, we hypothesized that there would be larger associations of the basic childhood vaccines with mortality than would be expected from their associations with cause-specific mortality alone.

METHODS

Data

We combined all publicly available data sets from the DHS for which we were able to measure child mortality, the vaccination status for all 5 basic vaccines in living children, and household wealth (which is based on an asset index). A list of the surveys used in the analysis is presented in Web Table 1 (available at http://aje.oxfordjournals.org/). The DHS are nationally representative samples, typically of persons 15–49 years of age, in developing countries, and they have been conducted since the 1980s (27).

Detailed birth histories that document all children born in the previous 5 years, as well as the current status of these children, are collected from women (26). Our sample included approximately 1 million births between 1985 and 2011 in 62 countries recorded in 149 surveys. Most DHS surveys include vaccination status for 1 dose of the BCG vaccine, 3 doses of the DPT vaccine, 3 doses of the polio vaccine, 1 dose of the measles vaccine, and 1 dose of the tetanus vaccine in mothers. We determined vaccination status based on either the vaccination card or, when unavailable, a report by the mother. Further details are presented in Web Appendix 1. A summary schedule for the relevant vaccines is presented in Table 1.

Because DPT and polio vaccinations are typically administered at the same time, we found that it was not possible to identify the individual associations of each type of these 2 vaccines with mortality, because children tended to have received both or neither, making the vaccines collinear. We combined DPT and polio into a single variable, with each dose considered to constitute 1/6 of a vaccine. Therefore, receiving a full schedule of DPT and polio resulted in a score of 1. For the other childhood vaccinations (BCG and measles), we constructed a binary variable for each child that indicated whether the child had received the relevant vaccine

Table 1. World Health Organization Vaccination Schedule

Vaccine	Typical Timing of First Dose	Recommended No. of Doses[a]	Usual Interval Between Doses
Bacillus Calmette-Guérin	At birth	1	
Diphtheria-pertussis-tetanus	6 Weeks	3	4 Weeks
Polio	Birth or 6 weeks	4/3	4 Weeks
Measles	9 or 12 Months	1/2	4 Weeks
Maternal tetanus	Pregnancy	Depends on vaccination history	

[a] More comprehensive accounts of coverage estimates (54) and data on when vaccines are to be administered for infant vaccines and for maternal tetanus are available from the World Health Organization (55, 56). Cost estimates for measles and maternal tetanus vaccinations are available from UNICEF (57, 58).

dose. In addition, women reported the number of tetanus toxoid injections that they received during their last pregnancy, and we used that as a child health intervention because immunity to tetanus is transferred to the child in utero (28). Because the recommended dose varies depending on vaccination history, we constructed an indicator for whether any tetanus vaccinations were received during each pregnancy. We did not find any association with a second tetanus vaccination. We had data on maternal tetanus injections only for the pregnancies in the past 5 years; therefore, information about tetanus vaccinations during prior pregnancies before this period was not included. Even if the mother was not injected during the most recent pregnancy, she could have had continuing immunity from the prior vaccinations, but we were not able to measure this in our data.

A complication is that childhood vaccination information in the DHS is typically collected only for children who are alive, which is a common limitation of survey data, and so we could not match child mortality data to childhood vaccinations at the individual level (except for maternal tetanus vaccination, which was recorded for all women in our sample). To avoid this problem, we aggregated the data on mortality and vaccination coverage to the level of the DHS primary sampling unit cluster. The DHS in each country adopts a multistage sampling approach that involves stratification first by region and then by urban and urban rural residence within each region (27). Potential sampling units are defined by geographic localities, usually enumeration areas from the most recent national census. Primary sampling units, our "clusters," are randomly selected from these enumeration areas within each strata. Once these primary sampling units are chosen, interviewers visit the area and sample a subset of the households in that location to identify and interview eligible respondents. When we aggregate our data to the cluster level, we are therefore calculating sample averages for localized geographic areas based on households that are in close proximity.

Because we expected an association between vaccination status and mortality, the vaccination rate among the children who have died may differ from the vaccination rate among the children who survive, and ignoring the missing data could induce selection bias in our estimates of cluster vaccination rates, as well as in our estimates of the association between vaccination status and mortality. Therefore, we implemented a correction based on Bayes' theorem (29) and an initial estimate of the relative risk of mortality for each vaccination type that we obtained from the data.

Correcting estimates of vaccination coverage for missing data

The proportion of children vaccinated in a particular cluster ($p(\text{vacc})$) is given by the vaccination rate among children who have died ($p(\text{vacc}|\text{dead})$) weighted by the proportion of children in that cluster who have died (Dead), plus the vaccination rate among the children who are alive ($p(\text{vacc}|\text{alive})$) weighted by the proportion of children in that cluster who are alive (Alive), as follows:

$$p(\text{vacc}) = p(\text{vacc}|\text{dead}) \times \text{Dead} + p(\text{vacc}|\text{alive}) \times \text{Alive}.$$

$p(\text{vacc}|\text{dead})$ is unobserved; however, using Bayes' theorem, we can write this expression as a function of the relative risk of mortality for vaccination status:

$$p(\text{vacc}|\text{dead}) = \frac{p(\text{dead}|\text{vacc}) \times p(\text{vacc})}{p(\text{dead}|\text{vacc}) \times p(\text{vacc}) + p(\text{dead}|\text{not vacc}) \times (1 - p(\text{vacc}))}.$$

Dividing above and below by $p(\text{dead}|\text{vacc})$, this equates to:

$$\frac{p(\text{vacc})}{p(\text{vacc}) + (1 - p(\text{vacc})) \times \text{RR}(\text{dead}|\text{not vacc})},$$

where RR(dead|not vacc) is the relative risk of mortality for those who were not vaccinated, given by $p(\text{dead}|\text{not vacc})/p(\text{dead}|\text{vacc})$. It follows that we can derive a correction to the observed vaccination rate using this relative risk to calculate the true vaccination rate in the cluster based on the solution to the following equation:

$$p(\text{vacc}) = \frac{p(\text{vacc})}{p(\text{vacc}) + (1 - p(\text{vacc})) \times \text{RR}(\text{died}|\text{not vacc})} \times \text{Dead} + p(\text{vacc}|\text{alive}) \times \text{Alive}.$$

Assuming that the proportions of dead and living children and the relative risk are known, we then have a single equation with 1 unknown (p(vacc)). The proportion of surviving children and the proportion of children who have died in each cluster can be obtained from the data; however, using the observed values in the calculation of the corrected vaccination rates is problematic. The proportion of children who have died, Dead = (1 − Alive), is essentially the dependent variable in our regression analysis, which is what we are trying to explain. Using the outcome directly as a component of our explanatory variable clearly opens the argument that the explanation is vacuous. More formally, the error term in our regression analysis clearly contributes to the outcome, and hence any explanatory variable that included the actual value of Dead as a component is going to be correlated with the error term, violating the assumptions required for estimation. Therefore, we replace these terms with the expected cluster mortality and survival rates (E(Alive) and E(Dead)), which we estimate from the Poisson model described below. These terms are functions of the existing explanatory variables alone, and correct, in expectation, the bias induced by only measuring the vaccination status of living children. Then, solving for p(vacc) using the standard quadratic formula, we obtain:

$$p(\text{vacc}) = \frac{-E(\text{Dead}) - p(\text{vacc}|\text{alive}) \cdot E(\text{Alive}) + \text{RR}(\text{died}|\text{not vacc}) + p(\text{vacc}|\text{alive}) \times E(\text{Alive}) \times \text{RR}(\text{died}|\text{not vacc})}{2(\text{RR}(\text{died}|\text{not vacc}) - 1)}$$
$$\pm \left\{ \frac{\left(\begin{array}{l} \sqrt{(-4 \times p(\text{vacc}|\text{alive}) \times \text{Alive} \times (\text{RR}(\text{died}|\text{not vacc}) - 1) \times \text{RR}(\text{died}|\text{not vacc})} \\ \quad + (E(\text{Dead}) + p(\text{vacc}|\text{alive}) - \text{RR}(\text{died}|\text{not vacc}) - \text{RR}(\text{died}|\text{not vacc}) \\ \quad - p(\text{vacc}|\text{alive}) \times \text{RR}(\text{died}|\text{not vacc})) \end{array} \right)}{2(\text{RR}(\text{died}|\text{not vacc}) - 1)} \right\}.$$

Table 2. Poisson Model Results for Cluster Vaccination Coverage and Cluster Mortality for Children Less Than 5 Years of Age in the Demographic and Health Surveys, 1985–2011[a]

Variable[b]	All Vaccines				By Vaccine Type			
	Raw Vaccination Coverage[c]		Corrected Vaccination Coverage		Raw Vaccination Coverage[c]		Corrected Vaccination Coverage	
	Adjusted Risk Ratio[d]	95% CI	Adjusted Risk Ratio[d]	95% CI	Adjusted Risk Ratio[d]	95% CI	Adjusted Risk Ratio[d]	95% CI
Mean vaccination	0.76	0.71, 0.81	0.73	0.68, 0.77				
Bacillus Calmette-Guérin					1.04	0.96, 1.12	1.03	0.96, 1.11
Diphtheria-pertussis-tetanus and polio					0.97	0.89, 1.06	0.97	0.89, 1.06
Measles					0.83	0.77, .89	0.83	0.78, 0.89
Maternal tetanus					0.92	0.86, 0.97	0.92	0.86, 0.97

Abbreviation: CI, confidence interval.

[a] Demographic and Health Survey data are available from www.dhsprogram.com. Regressions are based on 68,490 primary sampling unit clusters, which were derived from 149 surveys in 62 countries, and 960,271 children.

[b] All variables are averages at the cluster level. The diphtheria-pertussis-tetanus and polio variable measures the proportion of children in the cluster who received the recommended dose of both (receiving all 6 doses gives a score of 1). Other vaccine variables are the cluster averages of the proportion of children who received the relevant vaccine. Mean vaccination is the average of the 4 vaccine variables. All models included country fixed effects and country time trends, year of birth, sex, place of birth, birth interval, mother's age, type of place of residence, mother's educational level, access to a flush toilet, access to piped water, mother's partner's educational level, mother's marital status, mother's religion, household wealth index, number of siblings, and whether the mother had antenatal visits for that pregnancy. We also controlled for the number of months between the interview and birth as a measure of exposure risk. The outcome is the number of deaths in children born in the previous 5 years in each cluster, and the Poisson model also includes the number of births in the previous 5 years in each cluster, with the relevant coefficient offset to 1.

[c] The raw vaccination coverage in a cluster is defined as the proportion of surviving children who are 1 year of age or older and have received the relevant doses. The corrected vaccination coverage is adjusted for missing data on children who have died.

[d] Coefficients illustrate the relative risk of mortality associated with moving from 0% vaccination coverage to 100% coverage.

This equation will have 1 root in the interval 0–1 (29). We can estimate each of the quantities on the right side of the equation above from the data and use this formula to obtain corrected estimates of vaccination coverage for BCG, DPT/polio, measles, and the mean vaccination rate for each cluster using the following procedure. We first estimate the relative risk of mortality (calculated as the ratio of predicted mortality for 0% coverage relative to 100% coverage), RR(died|not vacc)$_0$, separately for each vaccination type using a Poisson regression model that is adjusted for covariates and the observed vaccination rates in each cluster. Then, we obtain the predicted mortality and survival rates in each cluster from this model (E(Alive) and E(Dead)), as well as the first iteration of the corrected estimate of vaccination coverage for each vaccine type in each cluster using this estimate of relative risk and the formula above. The relative risk for vaccination type is then recalculated using the corrected coverage rates. We perform this procedure over 10 iterations to obtain a final estimate of corrected coverage and a final estimate of the relative risk, RR(died|not vacc)$_{10}$. Overall, the coverage rates are not much affected by the omission of data on children who have died; in particular, the estimated coverage rates barely change after the first iteration, as shown in Web Table 2. In general, this will be the case unless both mortality and the relative risk of mortality from not being vaccinated are very high. We use these corrected coverage rates as our independent variables in the model presented in Table 2.

Poisson regression model

This approach, in which we aggregate at the cluster level, gives us 68,490 observations. We excluded an additional 79 clusters for which the predicted mortality was 100%, because this would have resulted in a corrected vaccination rate of 0% for these clusters. However, we have verified that our results are not sensitive to their inclusion. Following the previous literature (30), we define the 4 vaccination rates in a cluster as the proportion of children who had survived to 12 months of age and who had received the relevant doses (a single dose for BCG and measles, the combined 6 doses of DPT and polio, and a tetanus shot for the mother during pregnancy); therefore, clusters without any children 12 months of age or older are excluded from the analysis. We estimate the average vaccination rate in a cluster as the mean of these 4 indicators. Web Figure 1 is a histogram showing the distribution of average vaccination coverage across clusters. Web Figure 2 is a scatterplot showing the vaccination coverage in each cluster and the corresponding vaccination coverage that has been corrected for missing data.

We use modified Poisson regression to estimate the relative risk for the average vaccination rate using the following model (31):

$$\lambda_c = \exp(\alpha + \beta\ \text{Vaccination Rate}_c + X_c'\gamma + \mu_c),$$

where λ_c is the number of children in the cluster who have died, α is a constant, Vaccination Rate$_c$ is the average vaccination rate in the cluster, β is the associated parameter measuring relative risk of vaccination coverage, X_c represents the independent variables measured at the cluster level, γ is the parameter vector associated with these control variables, and μ_c is an error term. X_c includes the number of births in the cluster with the coefficient offset to 1 so the number of child deaths is proportional to the number of births and the other explanatory variables affect the mortality rate. We included deaths of children younger than 1 year of age in our outcome (even though they may have been too young to have received all basic vaccinations) to capture potential spillover effects; however, when we excluded children in this age group, we found very similar results. The advantage of the Poisson model is that it allows us to estimate the relative risk directly. Using the estimated regression parameters $(\hat{\alpha}, \hat{\beta}, \hat{\gamma})$ from our Poisson model, the expected mortality rates for use in our correction for missing data can then be obtained from:

$$\widehat{E(\text{Dead})}_c = \frac{\exp(\hat{\alpha} + \hat{\beta}\ \text{Vaccination Rate}_c + X'_c\hat{\gamma})}{\text{Number of Births}_c}.$$

We also estimate the relative risk for each of the 4 vaccination types (BCG, DPT/polio, measles, and maternal tetanus) using a model in which we control for all 4 vaccination types simultaneously.

A potential concern with our model is that the vaccination and mortality rates could be correlated with some other feature of the cluster that we are unable to adequately measure, such as underlying disease environment (32). If this omitted variable is correlated with vaccination coverage, our estimates of the association of vaccination coverage with mortality could be biased. We controlled for this to the extent possible using measured covariates in the clusters. Web Table 3 shows the results excluding covariates other than country fixed effects and country trends, and Web Table 4 gives the full results showing coefficient estimates for all covariates.

RESULTS

Table 2 presents results for vaccination coverage using the Poisson regression model described above, with cluster child mortality incidence (number of child deaths) as the dependent variable and with adjustment for other cluster characteristics. The corrected vaccination coverage columns present results using coverage rates that were adjusted for missing data on children who have died. Using the raw coverage rate, an increase in the mean vaccination coverage was associated with a relative risk of 0.76; that is to say, moving from 0% coverage to 100% coverage for all vaccination types (BCG, DPT/polio, measles, and maternal tetanus) was associated with a decrease in cluster level mortality of 24%. The data that are corrected for the selection effect of not measuring vaccination status of the dead children imply a slightly lower relative risk of mortality of 0.73.

We also implemented a model in which we tested whether the mix of vaccines affects mortality (Table 2). The mix of vaccinations in a cluster is likely to depend on the available supply and factors such as donor funds or campaigns initiated as part of supplementary immunization activities (10, 33). Under the "by vaccine type" heading, the first set of estimates disaggregates the vaccination types, and the second set does the same using the vaccination data that have been corrected

for mortality selection. The results indicate that measles vaccination is associated with a relative risk of mortality of 0.83, whereas maternal tetanus vaccination is associated with a relative risk of 0.92. Thus, most of our estimated association of overall vaccination with cluster mortality comes from these 2 vaccines; the associations with the BCG vaccine and with the combination of the DPT and polio vaccines appear to be very small.

DISCUSSION

Our results imply that vaccination coverage has a substantial association with under-5 mortality at the cluster level, particularly for measles and maternal tetanus vaccination. These results are consistent with recent evidence of the nonspecific effects of vaccines from previous observational studies, animal studies, and randomized control trials (34, 35). There are therefore likely to be substantial reductions in child mortality associated with further increases in vaccination coverage, particularly additional immunization associated with measles and maternal tetanus in sub-Saharan Africa, where vaccination rates lag behind those in other regions (11).

Our population-level estimates provide new evidence of the association between all-cause mortality and coverage of basic childhood vaccinations using nationally representative samples in diverse settings across 62 countries. Generally, it is not possible to estimate the association between vaccination status and mortality at the individual level in household survey data, such as the DHS, because the vaccination status of children who have died is not usually reported (36). Our approach of aggregating the data and correcting for this potential selection bias allows us to estimate this relationship at the cluster level. An additional advantage of this aggregate analysis is that it allows us to capture potential herd immunity (37–39), which would not typically be observed in an individual-level analysis. Moreover, our focus on all-cause mortality avoids the issue of misreporting of cause of death that can be seen in studies that use cause-specific mortality (40) and allows for the possibility of nonspecific effects of vaccination. There is typically substantial variation in vaccination coverage within countries and even within regions (11), and conducting the analysis at these higher levels of aggregation will mask this heterogeneity and potentially attenuate estimates of the association of interest. DHS clusters are small geographic areas, and therefore the households in each cluster are in close proximity, making this the ideal unit of analysis to investigate the full association of vaccine coverage with mortality. Demonstrating that similar estimates are obtained from a variety of different estimation strategies in a variety of different populations strengthens the case for increasing vaccination coverage as an effective intervention to improve child health in low- and middle-income countries (41).

Worldwide, the annual decrease in the under-5 mortality rate from 1990 to 2010 was 2.1%, whereas a decrease of 4.4% was necessary to meet the fourth Millennium Development Goal (42). Results in this paper imply that the basic vaccines provide a viable means of achieving progress toward this target of reducing child mortality. Global child mortality fell from 8.8% in 1990 to 5.7% in 2010, or from 12 million annual deaths to 7.6 million annual deaths (43). Over the same time period, the corresponding global coverage rate for measles vaccination rose from 73% to 84% according to World Health Organization estimates. The corresponding estimate from our sample indicates that 64% of children were vaccinated against measles in 1986–1990, compared with 84% in 2006–2010. We were unable to find global estimates for coverage of maternal tetanus vaccinations for the relevant time period; however, our data indicate that 56% of children had mothers who had been vaccinated for tetanus before pregnancy in 1986–1990, compared with 60% in 2006–2010. The estimates from Table 2 imply that the increases in coverage of the measles and tetanus vaccines combined were responsible for a 3.7% fall in global mortality. The mean vaccination rate in our data increased from 65% in 1986–1990 to 81% in 2006–2010, which corresponds to a reduction in mortality of approximately 4.5%. Overall, coverage estimates indicate that there is substantial scope for further increasing vaccination rates (44), particularly in sub-Saharan Africa.

It is reasonable to ask whether expanding coverage of measles and maternal tetanus vaccinations would be cost-effective strategies for reducing child mortality. If measles vaccination coverage could be raised a further 16 percentage points to 100%, this would equate to roughly a 3% reduction in mortality, or an estimated reduction of approximately 210,000 deaths (43). For maternal tetanus vaccination, our estimates imply that increasing immunization coverage by 40 percentage points to 100% would result in approximately 240,000 fewer deaths.

According to estimates from the United Nations, the lowest cost of a single dose measles-mumps-rubella vaccine is $2.05, whereas the lowest cost for a maternal tetanus vaccine is $0.05 (see the note to Table 1 for further details). Under the simplifying assumption that raising measles vaccination coverage by 16% would require an extra 133 million × 16% = 21 million doses and a 21 million × 2.05 = $43.05 million expenditure, the resulting approximate cost per life saved would be 43.05 million/210,000 = $205. Likewise, for tetanus, assuming that raising coverage by 40% would require an additional 133 million × 40% = 53 million doses and a 53 million × $0.05 = $2.7 million expenditure, the resulting approximate cost per life saved would be 2.7 million /240,000 = $11.

Although these calculations are based on highly simplified assumptions and only account for the cost of vaccines themselves and not administration or roll-out of expanded programs, these figures nevertheless provide some indication that increases in vaccination coverage as a means to reduce child mortality and achieve the targets laid out in the Millennium Development Goals are likely to be highly cost effective, particularly for maternal tetanus immunization. For example, the estimated per-person cost for full immunization for BCG, DPT, polio, and measles in the Global Alliance for Vaccines and Immunization countries was $4 in 2011 (45). Moreover, estimates based solely on direct health benefits might understate the value of vaccines because there are likely to be additional benefits to society above and beyond their protective effects on mortality (46–48). For example, in previous studies, investigators have linked increases in vaccination coverage to improvements in human capital (49, 50).

There are important limitations associated with estimating the association between vaccination status and mortality from

household surveys (32), and future research should adopt methods for further validating the causal relationship between immunization and mortality, with particular emphasis on the drawbacks of using mother-reported vaccination status and the role of potential omitted confounding. Our results are somewhat smaller than the limited available evidence on nonspecific effects of vaccines from randomized control trials (51); however, this is likely to reflect a number of drawbacks to the data. First, we estimated cluster-level vaccination coverage from the survey, which could have introduced measurement error and attenuation bias. Second, we did not consider the timing or ordering of vaccinations (21). Third, we did not examine potential interactions or nonlinearities in the data. Vaccine efficacy might vary with country-, cluster-, family-, and child-level characteristics (52). The literature has documented potential modification by sex and receipt of vitamin A supplementation (17, 53). Finally, our estimates come from data that are only nationally representative, not globally representative. The results in this paper should be interpreted with these limitations in mind.

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