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Measles mortality in high and low burden districts of India: Estimates from a nationally representative study of over 12,000 child deaths

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ABSTRACT

Background: Direct estimates of measles mortality in India are unavailable. Our objective is, to use a nationally-representative study of mortality to estimate the number and distribution of, measles deaths in India with a focus on 264 high burden districts.

Methods: We used physician coded verbal autopsy data from the Million Death Study which surveyed, over 12,000 deaths in children aged 1 month to under 15 years from 1.1 million nationally, representative households in 2001–2003.

Results: We estimate there were 92,000 (99% CI 63,000–137,000) measles deaths in children 1–59, months of age in India in 2005, representing a mortality rate of 3.3 (99% CI 2.3–5.0) per 1000 live, births and about 6% of all 1–59 month deaths. In children under 15 years of age, there were 107,000, (99% CI 74,000–158,000) measles deaths. The measles mortality rate was nearly 70% greater in girls, than in boys, and 60% of the deaths were in three populous states Uttar Pradesh, Bihar, and Madhya Pradesh. The 1–59 month measles mortality rate in high burden districts was 4.48 (99% CI 3.94–5.02) compared to 2.40 (99% CI 2.28–2.52) per 1000 live births in other districts.

Conclusion: Measles killed over 100,000 children in India in 2005 and girls were at higher risk than boys. The majority of measles deaths occurred in a few states and high burden districts. The results of this study highlight the importance of focusing measles supplementary immunization activities in high burden districts.

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1. Introduction

Despite the availability of a safe and effective measles vaccine for more than four decades, measles continues to be a major cause of mortality in children. The World Health Organization (WHO) estimated that in 2004 there were 424,000 deaths due to measles in children under-5 years of age, of which a third (142,000) were estimated to be in India [1,2]. Recent mathematical modeling, based largely on measles surveillance, has estimated that between 2000 and 2010, measles deaths in India decreased by only 26% compared

to 78% for the rest of the WHO South East Asia region [3]. The most recent estimates from the WHO suggest that measles deaths decreased by only 36% between 2001 and 2011 [4]. Both estimates suggest that India remains the country with more measles deaths than any other and approximately a third of the world's measles deaths [3,4].

Measles vaccine was first included in India's Universal Immunization Program (UIP) in 1985, and by 1990 the UIP included all districts in the country. In 2004, India launched a measles mortality reduction strategic plan that targeted high routine measles vaccination coverage of infants 9–12 months of age. However, an optimal targeting of the national measles strategy was hindered in part because official reporting of the disease and related deaths dramatically underestimated the true burden. In 2004, based on the country's measles surveillance system, there were approximately 50,000 reported cases of measles infection and only 140 reported

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deaths in the entire country, suggesting that only approximately 1 in 1000 measles deaths were captured [5]. In 2010, India started a second opportunity for measles immunization through either a second routine dose of measles vaccine or through supplemental immunization activities (SIA), the latter starting in specifically identified high burden districts that were defined as lagging in multiple health indicators including infant and maternal mortality, disease burden, and effectiveness of policies [5,6].

To help refine immunization programming and to maximize the impact of a second-dose strategy, we present here national and sub-national estimates of the distribution of measles mortality generated from a nationally representative survey of deaths from 1.1 million households. Special attention is paid to the government-identified high burden districts.

2. Methods

The survey methods used in the Million Death Study (MDS) are well described elsewhere [7,8]. In brief, the MDS is conducted within the Registrar General of India's (RGI) nationally representative Sampling Registration System (SRS), which is a large, routine, demographic survey that has served as the most reliable source of information on fertility and mortality in India since 1971. The SRS sampling frame used for this study surveyed 63 million people in 11 million nationally representative Indian households for causes of death between 2001 and 2003 [9]. The survey included 6671 sampling units chosen randomly to be representative at the urban and rural level for the major states of India. An average of 150 households were selected from each unit and each selected household was monitored for vital events on a monthly basis by a part-time enumerator and every 6 months by a full-time surveyor from the RGI. Each death in the MDS database was identified by an enhanced method of verbal autopsy (VA) termed RHIME (Routine, Reliable, Representative and Re-sampled Household Investigation of Mortality with Medical Evaluation) [10]. Information on the details of the death was collected through questionnaires using both an open-ended narrative and close-ended questions administered by trained surveyors. Questions on the RHIME that were specific to measles included the presence, location and progression of rash, cough, fever, and whether the illness was measles using locally accepted, language-appropriate terms for "measles". As the VA was designed to identify all causes of death and not just measles, it did not systematically ask regarding the timing of symptoms and signs of measles in relation to the death although these details may have been included in the narrative. Two physicians independently reviewed each completed RHIME and assigned a single cause of death using the International Classification of Disease-10 (ICD-10) [11]. The death was classified as measles if at least one physician coded it as such. Deaths were classified using the ICD-10 based classification of causes of death as previously described in our study of under-5 mortality in India [7].

To determine population and mortality envelopes, total population and deaths among boys and girls aged 1–59 months at the state level and by rural and urban areas were proportionally corrected to reflect the UN Population Division estimates for India in 2005 [12]. We chose 2005 as the reference year due to its proximity to MDS data collection (2001–2003), to minimize the impact of demographic and immunization program changes over time, and the availability of UN population estimates. All proportions were weighted to account for the survey sampling design. Mortality rates per 1000 live births were calculated for each gender, state, and region, and for high burden and low burden districts [7]. The 99% confidence intervals for all estimates of proportions of causes of death were based on the observed number of deaths in the study and the survey design and sampling. District level

population envelopes were developed by our group for another study and were based upon 2010 population. To remain consistent with the 2005 reference year in this study, we adjusted the district level analysis for 2005 population. The population and mortality envelopes for district level analyses used multiple data sources [13]. We first obtained infant and under-5 mortality rates for each district using data on children ever born and children surviving from India's District Level Household Survey (DLHS) 2 (2002–04), DLHS-3 (2007–2008), the South Asian Mortality Pattern, and the UN MORTPAK4 software [14]. Estimated infant mortality rate was then portioned into neonatal mortality rate and post-neonatal mortality rate based on the share of neonatal deaths and post-neonatal deaths in the total infant deaths for each district as tabulated in DLHS-2, DLHS-3, Special Fertility and Mortality Survey (1998), and MDS data (2001–2003). We then obtained proportional share of each event for districts within each state and applied them on the estimated state live births and deaths for the year 2010 to obtain district envelopes.

High burden districts were defined as the 264 districts identified by the Government of India as lagging behind on specified health parameters and low burden districts were the remaining 342 districts [15]. Total deaths, measles deaths, and measles mortality rates in the high and low burden districts were calculated for boys and girls.

This study has been approved by the review boards of the Post-Graduate Institute of Medical Education and Research, the Indian Council of Medical Research, the Indian Health Ministry's Screening Committee, and by St. Michael's Hospital in Toronto, Canada.

3. Results

There were a total of 758 deaths in the MDS sample attributed to measles in children 1–59 months of age and an additional 161 in children aged 5–14 years (Table 1). There was not a significant difference in the number of measles deaths per year of MDS data collection. Approximately 90% of these deaths occurred in rural areas and fewer than 10% occurred in health care facilities. From these data, we estimate that in India in 2005 there were approximately 92,000 (99% CI 63,000–137,000) measles deaths in children aged 1–59 months and another 15,000 (99% CI 11,000–21,000) measles deaths in children aged 5–15 years. The 1–59 month measles mortality rate was 3.3 (99% CI 2.3–5.0) per 1000 live births. Thus, approximately 1 in 300 children born in India in 2005 died from measles.

While the proportion of all deaths that were due to measles was less than 1% in most districts in the southern half of the country, the measles proportional mortality exceeded 5% and even 10% for both boys and girls in many districts in the northern half of the country where most of the high burden districts are located (data not shown). More than 75% of all measles deaths occurred in the central and east regions (Fig. 1). The majority of 1–59 month deaths occurred in just six states (Fig. 2): Uttar Pradesh (35,300); Bihar (10,600); Madhya Pradesh (8100); Gujarat (4700); Rajasthan (4300); and Haryana (1900). Uttar Pradesh was the location of nearly 40% of all 1–59 month measles deaths.

There were large differences in measles mortality by gender. Overall, there were nearly 50% more deaths in girls 1 to 59 months than in boys (56,000 vs. 36,000) and the overall measles mortality rate was nearly 70% higher in girls (4.2 vs. 2.5 per 1000 live births). The mortality rate from measles was higher in girls than in boys for each region studied, ranging from 27% higher in the northeast to more than twice as high in the west (Fig. 1).

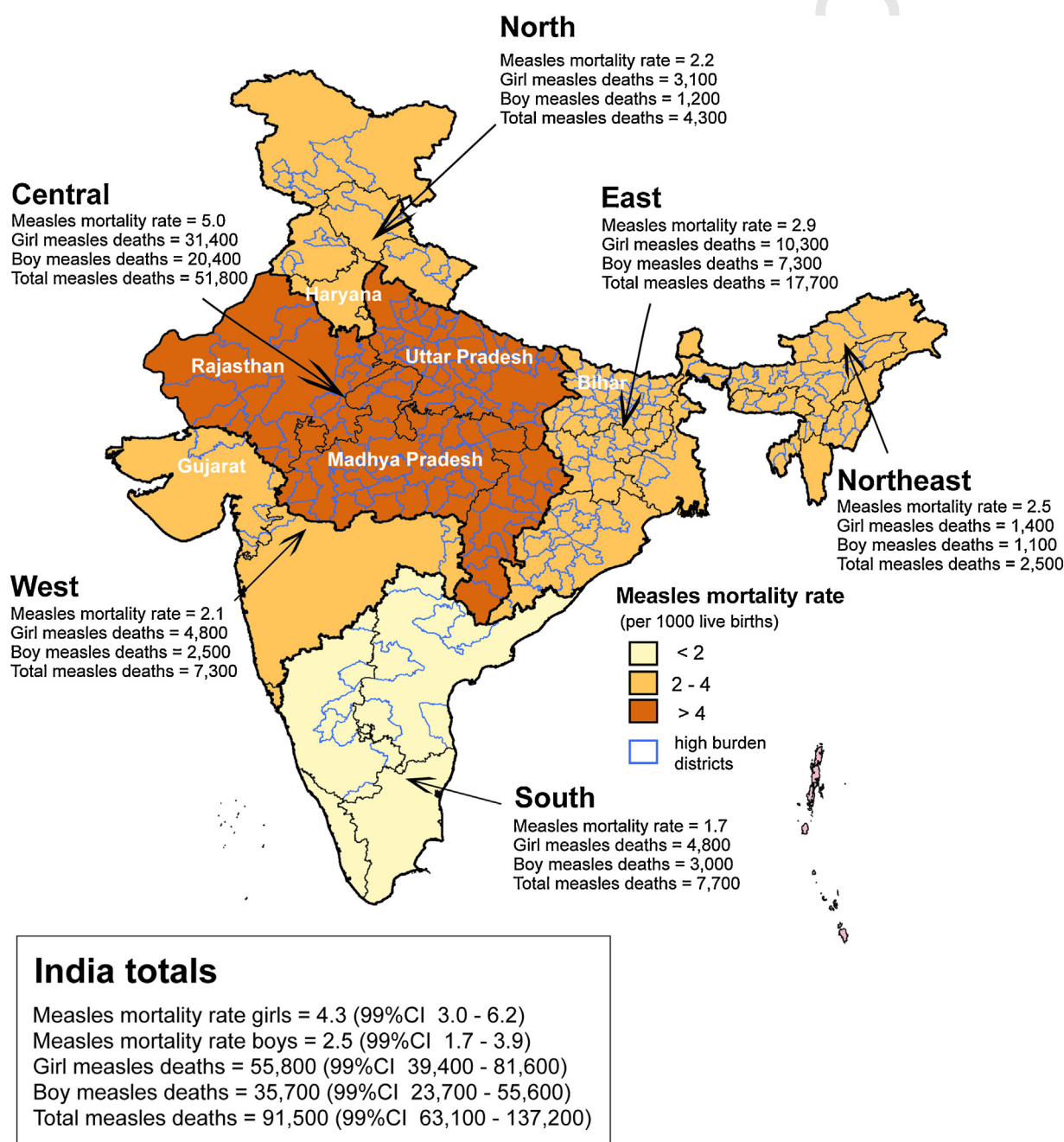
To further explore difference in measles mortality, we analyzed 1–59 month measles mortality rates in the 264 high burden districts compared to all other districts. The 1–59 month measles

Table 1

Under-5 year old MDS measles study deaths (2001–2003) and estimated 2005 India measles mortality rate and total deaths.

Age	Measles study deaths, 2001–2003					Estimated measles deaths, all India, 2005					
	Boys	Girls	Total	Rural area (%)	Died in health facility (%)	Mortality rate ^a			Total deaths (thousands)		
						Boys	Girls	Total (99% CI)	Boys	Girls	Total (99% CI)
1–11 mo	90	125	215	192 (89)	21 (10)	0.6	1.2	0.9 (0.5–1.6)	9	16	24 (14–45)
12–59 mo	218	325	543	495 (91)	43 (8)	1.9	3.0	2.4 (1.8–3.4)	27	40	67 (49–93)
1–59 mo	308	450	758	687 (91)	64 (8)	2.5	4.2	3.3 (2.3–5.0)	36	56	92 (63–137)
5 to <15 years	54	107	161	146 (91)	14 (9)	3.9	8.5	6.1 (4.5–8.5)	5	10	15 (11–21)
1 mo to <15 years	362	557	919	833 (91)	78 (8)	20.7	36.2	28.1 (19.4–41.5)	41	66	107 (74–158)

^a Mortality rate for children 1–11 months, 12–59 months, and 1–59 months is expressed as rate per 1000 live births. Mortality rate for children 5 to <15 years and 1 month to <15 years is expressed as rate per 100,000 population in age category.

**Fig. 1.** Regional distribution of under-5 measles deaths, India, 2005.

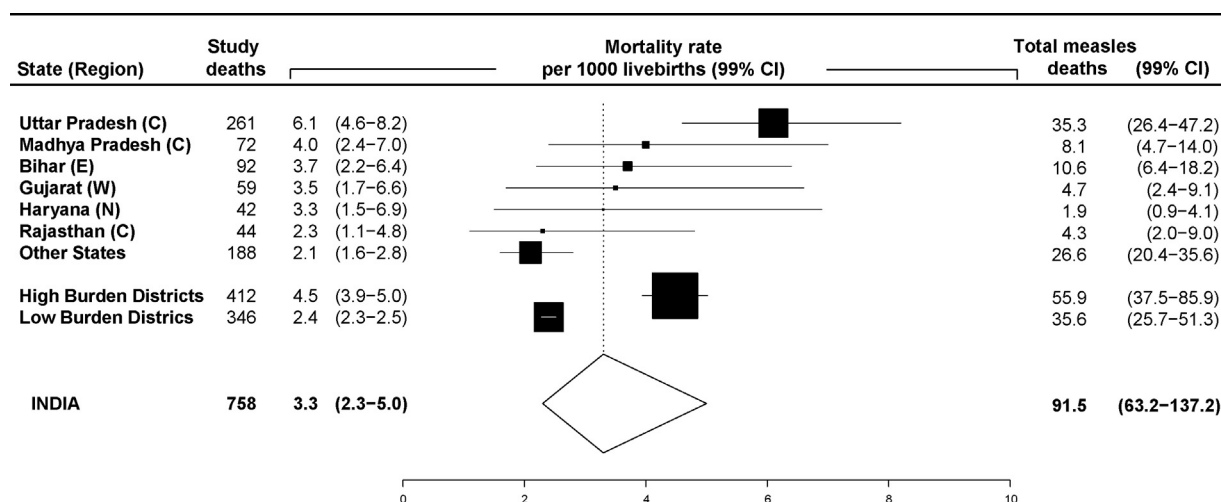


Fig. 2. Estimated 1–59 month measles mortality and total estimate deaths, India, 2005.

mortality rate for the high burden districts was 4.5 per 1000 live births (99% CI 3.9–5.0, absolute measles deaths 55,900) compared to 2.4 per 1000 live births (99% CI 2.3–2.5, absolute measles deaths 35,600) in all other districts. In both the 264 high burden and other districts there existed a large gender difference in measles mortality, respectively, 75% and 59% higher in girls than in boys.

India's DLHS-2 survey, conducted in 2002–2004 (overlapping with data collection in the MDS), found overall national measles immunization coverage of only 54%. The measles vaccination coverage in the 6 states identified in this study as having the greatest number of measles deaths ranged from 27% to 65% (Bihar 27%, Uttar Pradesh 35%, Madhya Pradesh 47%, Rajasthan 36%, Haryana 65%, Gujarat 65%) [16]. The DLHS-3 survey was conducted in 2007–2008 and did show an improvement in measles immunization coverage overall (68%) (Fig. 3) and in each of the high mortality states (Bihar 54%, Uttar Pradesh 47%, Madhya Pradesh 57%, Rajasthan 67%, Haryana 69%, Gujarat 73%) [17]. Significantly, the states with the lowest coverage rates showed the greatest improvements. However, all remained at sub-optimal levels for interrupting measles transmission. Even within states, measles-containing vaccines (MCV) coverage was not homogenous (Fig. 3). Examining at the district level, MCV immunization rates were lower than in high burden than low burden districts. In the DLHS-2, the MCV coverage was only 37.7% in high burden districts compared to 65.6% in other districts. While substantial improvements in MCV coverage occurred between DLHS-2 and DLHS-3, the coverage in high burden districts (57.9%) remained substantially below that in other districts (79.0%). In both DLHS-2 and DLHS-3, the proportion of girls immunized with MCV was lower than for boys in all of the highest burden states (Table 2). Of the 264 high burden districts, 137 are located in the 6 highest burden states identified in this study.

As a sensitivity analysis, we also used a stricter definition of measles that required both physicians reviewers of the VA to initially agree on the cause of death being measles. Using this method results in a national estimate of 68,000 deaths due to measles before age 5.

4. Discussion

We estimate that there were approximately 92,000 (99% CI 63,000–137,000) deaths due to measles in children aged 1–59 months in India in 2005. We estimate that there were a further 15,000 deaths (99% CI 11,000–21,000) in children 5 to under 15 years of age. The majority of deaths took place in a few of the large,

poorer states and in particular, within the 264 specific districts identified as lagging behind others with regards to other health outcomes. Approximately 90% of measles deaths occurred in rural areas and fewer than 10% occurred in health facilities.

Approximately three quarters of all Indian measles deaths occurred in 6 states that extend in a band across the north central portion of the sub-continent. Uttar Pradesh is the site of both the greatest number of measles deaths (35,000 (99% CI 26,000–47,000) and the highest measles mortality rate (6.1 (99% CI 4.6–8.2) per 1000 live births). Four of the states with high measles mortality, Uttar Pradesh, Madhya Pradesh, Bihar, and Rajasthan, have been identified by the Government of India as being part of the Empowered Action Group and Assam (EAGA) cluster of states that have lagged behind the rest of the country in most development indicators. The EAGA states have previously been identified as having higher all-cause mortality than other states as well as cause-specific mortality including deaths attributed to pneumonia and diarrhea [7].

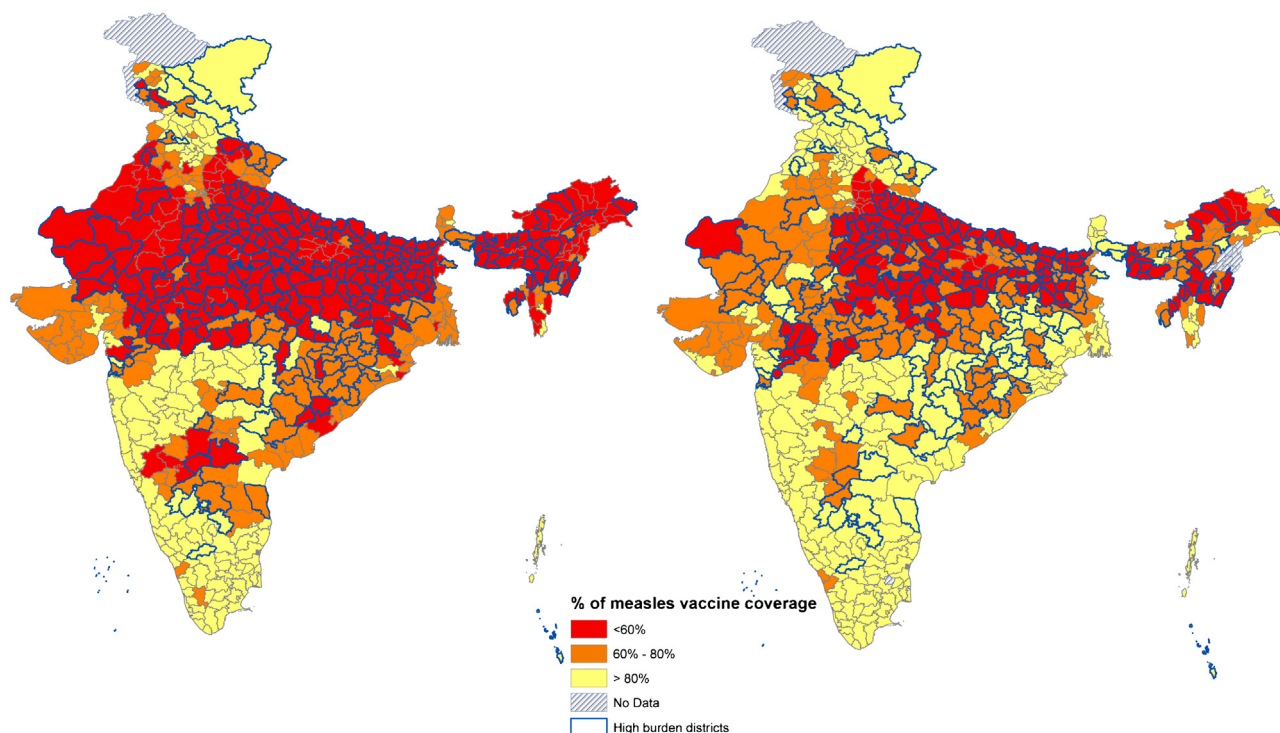
In 2004, the Government of India released a measles mortality reduction strategic plan that acknowledged that sub-optimal measles surveillance systems, particularly in states with low immunization coverage, resulted in gross underestimates of the number of cases and deaths and also in a lack of information regarding sub-national, age, and gender related distribution [5]. The MDS is a representative sample of deaths from India, including rural areas that are the location of the large majority of measles deaths and which are systematically under-represented in existing measles reporting. Thus, using these data, this study begins to address these information gaps.

In India, many health policy decisions are made and administered at the district level, thus it was important that the Government of India highlighted 264 districts that lag behind others in various health outcomes. In this study, we showed higher rates of measles mortality for both boys and girls in these 264 high burden districts. The identification of sub-state level administrative districts with low rates of MCV immunization and high rates of measles mortality allows the possibility for fine-tuning the intervention strategy.

The live attenuated measles vaccine is the most important tool in preventing infection and death from measles. A single dose of measles-containing vaccine (MCV1) is estimated to induce protective immunity in 85% of children who receive the vaccine at 9 months of age and 90–95% if vaccinated at 12 months of age [18]. Due to its highly infectious nature, it has been estimated that population level immunity against measles needs to be at minimum

DLHS2 (2002–4)

DLHS3 (2007–8)

**Fig. 3.** Percent of children aged 12–23 months receiving MCV1 [16,17].

93–95% to interrupt virus transmission [18,19]. The WHO strategy for measles mortality reduction includes the administration of a second dose of measles-containing vaccine (MCV2), optimally given between 15 and 18 months of age [19]. The rationale for providing a second opportunity for measles vaccination includes immunization of children who experienced primary vaccine failures as well as those who missed the first dose. WHO and UNICEF have noted greater success in reducing measles deaths in Africa than in India, largely because of ongoing low MCV1 coverage in high burden districts and, with the exception of a small number of select states, not having adopted the use of MCV2 [3,20].

In May 2010, the Government of India announced its decision to introduce MCV2 into the national program [21]. In 14 states where current overall coverage is estimated to be less than 80% (Arunachal Pradesh, Assam, Bihar, Chhattisgarh, Gujarat, Haryana, Jharkhand, Madhya Pradesh, Manipur, Meghalaya, Nagaland, Rajasthan, Tripura, and Uttar Pradesh), MCV2 is now being given to children via periodic mass catch-up vaccination campaigns. These campaigns target all children aged 9 months to before their tenth birthday regardless of their previous immunization or disease history [22]. In order to establish local best practices, the

initial phase of the catch-up vaccination campaign is being conducted in 45 districts in the selected states prior to scale up [22]. Notably, measles outbreaks continue to occur in India until the present day. There were more identified in 2012 than in 2010, the year MCV2 was introduced, reinforcing arguments for ongoing vigilance in maintaining high levels of MCV coverage and for strong surveillance systems [23]. Our study shows significantly higher mortality rates in high burden districts and confirms that a strategy targeting these districts is likely to be the optimal approach.

The gender discrepancies we identified in measles mortality are striking. Overall, the risk of measles deaths for girls aged 1–59 months was nearly 70% higher than for boys and the risk was higher in girls in both high burden and other districts. Previous studies have shown girls in India to be at higher risk than boys for all-cause mortality as well as for many infectious causes of death [7,24]. The reasons for higher all-cause mortality rates in girls are multifactorial and include worse overall nutrition [25], lower levels of vitamin A supplementation [16,17], lower likelihood of being brought to medical attention, and lower frequency of receiving appropriate antibiotic therapy for complications such as pneumonia, compared to boys [25]. However, a major factor contributing to higher measles

Table 2

Difference in MCV1 immunization coverage (%) by gender, 2002–2004 [16] vs. 2007–2008 [17].

High burden measles States	2002–2004			2007–2008		
	Boys (%)	Girls (%)	Difference (%) ^a	Boys (%)	Girls (%)	Difference (%) ^a
Bihar	29.2	24.0	5.2	57.4	50.6	6.8
Gujarat	64.7	64.7	0.0	73.0	72.1	0.9
Haryana	67.5	62.8	4.7	70.9	66.7	4.2
Madhya Pradesh	48.4	44.9	3.5	57.7	57.1	0.6
Rajasthan	38.6	32.4	6.2	70.0	64.3	5.7
Uttar Pradesh	37.3	32.7	4.6	48.8	44.8	4.0
Other States	72.0	70.5	1.5	83.5	82.9	0.6
All India	55.5	32.7	3.0	69.0	66.8	2.2

^a Difference = boy measles immunization coverage minus girl measles immunization coverage.

mortality in girls is likely to be lower measles immunization rates. In addition to DLHS 2 and 3, three major Indian National Family Health Surveys between 1992 and 2006 showed significantly lower measles coverage for girls [26]. While the overall measles immunization rates in the 6 highest mortality states identified by this study have increased between 2002 and 2008, girls continued to have lower MCV coverage rates than boys in each state (Table 2). If India were to achieve gender equality in MCV rates and if the measles mortality rate in girls was equal to that in boys, there would be nearly 20,000 fewer girls that would die of measles.

Ideally, a study on measles mortality would use a case definition based on microbiologically or physician confirmed cases. However, due to the epidemiology of measles in India, this is not possible and in light of the under-identification of measles through surveillance systems, we believe a nationally representative sample of VA identified deaths remains the optimal means of estimating measles mortality. The main limitation of this study is the potential misclassification of measles deaths to other causes and vice versa. Because only 8% of the deaths measles deaths occurred in health facilities, comparisons to hospital based studies for verbal autopsy can be fundamentally flawed [27]. However, in comparison with hospital deaths, the ability of verbal autopsy to distinguish measles deaths from respiratory infections and diarrheal diseases, has been reasonable; studies from the Philippines [28], Kenya [29], and Namibia [30], using different diagnostic algorithms, found sensitivities ranging from 67 to 98% and specificities ranging from 85 to 99% for measles deaths identified by verbal autopsy compared to hospital/physician diagnosis. For all MDS studies, we have adopted a less strict measles definition that required only one of two reviewing physicians to code a measles death (which would be expected to raise our sensitivity at the expense of specificity). We cannot calculate a sensitivity or specificity of our VA in determining measles as cause of death as this would require a gold standard (i.e. microbiologic or physician certified death) which is not available when the large majority of deaths occur in rural areas and outside of the health care system. The VA was designed to identify all causes of death in children and thus while it did include several measles specific questions, e.g. presence of rash, cough, was this measles (in the local language), it did not ask specific questions regarding exposures, duration of rash, and timing of symptoms in relation to each other and the time of death. The MDS identifies only deaths and thus we are not able to determine neither the number of measles cases nor the case fatality rate from these data. The MDS is a single cause VA based study meaning only the single most responsible underlying cause of death is recorded. Thus, we are not able to comment on the number of measles deaths whose proximal cause was a complicating pneumonia or diarrheal illness. The full VA used for this study may be seen at the Center for Global Health website [10]. While there are expected to be annual and seasonal fluctuations in incident measles cases, exploration of this issue is beyond the scope of this paper, however, it will be explored in a future mathematical modeling study based on MDS data and using more recent MDS data as it becomes available.

5. Conclusion

Measles remains a major killer of Indian children and that these deaths occur disproportionately in girls and are located in high burden districts in a small number of states in India. The identified discrepancies in measles mortality by gender and location clearly suggest populations that should be targeted to achieve higher vaccination rates and ultimately reduce measles related mortality. Through the recent introduction of a second dose of measles-containing vaccine in measles-endemic districts of high burden states, along with ongoing improvements in nutrition, access to

care, and other factors, India has taken important steps toward lowering the country's mortality burden. It will now be critical to measure the impact of these changes. The results of this study, which uniquely define measles mortality burden by age, gender, and geography, can serve as the definitive baseline benchmark against which these future gains can be measured.

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Conflicts of interest

None declared.

Author contributions

SKM, MN and PJ conducted the statistical analyses. All authors contributed to the collection and analysis of the data, and to the preparation of the report. All authors had an opportunity to contribute to the interpretation of the results and the drafting of the report and accept full responsibility for the content of this paper. SKM is the guarantor.

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