REVIEW ARTICLE

Measles Case Fatality Ratio in India: A Review of Community Based Studies

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Context: Measles remains a major cause of child mortality in India. Measles case fatality ratios (CFRs) vary substantially between countries and even within the same community over time. We present a review of Indian community-based measles CFR studies conducted from 1975 to 2008.

Evidence acquisition: PubMed, Cochrane Libraries, and all WHO databases were searched using a combination of terms. All community-based studies were abstracted into a database.

Results: We identified 25 studies with data on 27 communities. The median CFR was 1.63 per 100 cases (Q1= 0.00 and Q3= 5.06). Studies conducted after 1994 had significantly lower CFRs (*P*=0.031). Studies in rural settings had significantly higher CFRs compared to urban studies (*P*=0.015). No differences were found by study design or outbreak/endemic setting.

Conclusions: This review suggests measles CFR may be declining in India. We hypothesize that increased measles vaccination coverage is the main factor contributing to the decline. Widespread vaccination increases both the average age of infection and the proportion of total measles cases previously vaccinated. Vitamin A treatment/supplementation is also likely to have contributed. In order to further reduce measles burden in India, vaccination and vitamin A treatment/supplementation coverage should be increased and a two dose vaccine strategy should be implemented in all areas.

Keywords: *Case Fatality Rate, India, Measles, Mortality, Vaccination.*

It is estimated that 174,000 measles deaths occurred in the Southeast Asian region during 2005, with a substantial proportion of this burden in India(1). The measles case fatality ratio (CFR) can be affected by numerous host factors including: age at infection, crowding, immuno-suppression, vaccination status, malnutrition, and vitamin A deficiency(2). As a result, measles CFRs vary substantially between countries and even within the same community over time.

In 1993, WHO issued a standard protocol to determine measles case fatality ratios in a community(3). Community based studies provide the best available data in the published literature on measles CFR. Studies from Indian hospitals or other health centers are likely biased, since measles cases with complications are likely oversampled(4). Passive surveillance (case report) studies are also prone to under-reporting of measles cases and deaths.

A recent measles CFR review of community based studies was published by WHO in 2008; however, the authors did not perform an in-depth analysis of CFRs for India(5). The most recent review of measles CFR for India was published in 1994(6). Since 1994, India has increased vaccine coverage and routine vitamin A treatment was introduced. Here we present our updated systematic review of Indian CFR of measles from community based studies published 1980-2008.

METHODS

We systematically reviewed all published literature from January 1, 1980 to December 31, 2008 to identify Indian community based measles studies with data on measles CFRs. PubMed, Cochrane Libraries, and all World Health Organization Regional Databases were searched in all languages using combinations of the terms: *India*, *measles*, *case fatality*, *death*, and *mortality*. Prospective cohort and cross-sectional studies were abstracted. Studies were included if the study participants were from a defined Indian population with data from 1975-2008. Hospital or healthcare centre based studies and passive surveillance were excluded since these populations are likely not representative of the general Indian population.

Measles disease and measles attributed deaths were classified by the authors of the included studies. Data abstracted from the studies included: a location description (State/Union territory and urban/rural study site), year, type of study, if data were collected during an outbreak, measles cases by age, and measles deaths by age. We present CFR by the specified age groups of <1 year, 1-4 years, 5-9 years and 10+ years in order to simplify study comparison. However, if study data did not allow for these groupings, we present the data as reported.

We first preformed a descriptive analysis of the studies and investigated differences by study location, outbreak setting, type of study, and year. We report the median CFR by group and in parenthesis report the 1st (Q1) and 3rd (Q3) quartiles. In order to test differences between groups, we utilized the Kruskal–Wallis test, a non-parametric method for testing equality of population medians among groups(7). Study year was dichotomized by before and after 1994, as this was the year the last Indian CFR review was published. A *P* value <0.05 was considered statistically significant for all analyses. Analyses were conducted using STATA 10.0 Special Edition (STATACORP, College Station, TX).

RESULTS

We identified 25 Indian community based measles CFR studies with data on 27 distinct communities from 12 States/Union territories (8-32). Two studies presented data for two distinct populations and results were entered into the database by population (26,28). Study descriptors and results are presented for the 27 community populations in ***Table* I**. Twenty of the studies were cross-sectional (74.1%) and most were conducted in rural areas (81.5%). In addition, most of the studies were performed during measles outbreaks (70.0%). A total of 8247 measles cases and 218 measles attributed deaths occurred in the studies (pooled CFR=2.64%). The mean CFR was 4.27% with a range of 0.00-31.25% and the median was 1.63 (Q1=0.00 and Q3=5.06).

Next, we analyzed the data for factors associated with measles CFRs. The median CFR for prospective studies was 1.91 (Q1=0.79 and Q3= 3.52), and 1.16 (Q1=0.00 and Q3=7.00) for cross-sectional studies; the difference was not significant (*P*=0.811). The CFRs for studies conducted in rural communities (median=2.79, Q1=0.20 and Q3=7.00) were significantly higher in comparison to urban studies (median=0.00, Q1=0.00 and Q3=0.00) (*P*=0.015). The median CFR for studies performed during measles outbreaks was 2.86 (Q1=0.00 and Q3=7.07), and 1.10 (Q1=0.00 and Q3=2.19) for endemic settings; the difference was not significant (*P*=0.183).

Only 6 studies with data on 7 populations separated measles CFR by age and as a result we were unable to perform a statistical analysis of trend by age; however, in ***Fig.*1** we present a line graph of the data (8,9,12,13,24,26). This graph suggests a decrease in measles CFR with age, but whether CFRs for <1 yrs and 1-4 yrs differ is not clear.

We also assessed changes in measles CFR over time. In ***Fig.*1,** we present CFRs by midpoint study year, which suggests a decline in CFR over time. We also determined that CFR for studies occurring before 1994 (median=2.71, Q1=0.20 and Q3=7.00) were significantly greater in comparison to studies conducted after 1994 (median=0.00, Q1=0.00 and Q3=1.16) (*P*=0.031).

DISCUSSION

Measles case fatality ratios are known to significantly differ between countries and vary within populations over time(5). We reviewed Indian community based measles CFR studies to investigate factors influencing CFR and changes in mortality over time. CFR data are essential for disease burden modeling and an updated review of CFR was needed.

TABLE I DESCRIPTION AND RESULTS OF INDIAN COMMUNITY BASED STUDIES CONDUCTED FROM 1975 TO 2008

Study	Location	Urban or rural	Population age	Outbreak	Years	Type of study*	Total measles Cases	Total deaths	Over all CFR	<1y CFR	1-4y CFR	5-9y CFR	>10y CFR	Other age groups
Dhanoa(8)	Punjab	Rural	<2 yrs		1970s	P	82	3	3.66	2.63				1-2y 6.82
Chand(9)	Uttar Pradesh	Rural	< 14 yrs		1974-86	P	411	9	2.19	7.27				1-3 y 1.69 4-14 y 0.83
Garai(10)	West Bengal	Rural	Children		1976-78	P	862	2	0.2					
John(11)	Tamil Nadu	Rural	< 10 yrs	Yes	1977-78	P	198	14	7.07					
Cherian(12)	Tamil Nadu	Rural	< 5 yrs	Yes	1979-80	C	78	8	10.26	9.09	10.45			
Vasudev(13)	Uttar Pradesh	Rural	<12 yrs		1980	P	266	9	3.38	0	6.5			
Swami(14)	Rajasthan	Urban	< 15 yrs		1980-81	P	731	10	1.37					
Jajoo(15)	Maharashtra	Rural	< 10 yrs	Yes	1982	P	113	0	0					
Sharma(16)	Rajasthan	Rural	< 5 yrs	Yes	1982	C	88	4	4.55					
Lakhanpal(17)	Punjab	Rural	< 14 yrs		1982-83	C	241	2	0.83					
Bhatia(18)	Nagaland	Rural	< 12 yrs	Yes	1983	C	515	14	2.71					
Rao(19)	Karnataka	Rural	< 5 yrs		1983	C	132	0	0					
Lobo(20)	Haryana	Rural	< 10 yrs		1984	P	430	7	1.63					
Sharma(21)	Rajasthan	Rural	< 14 yrs	Yes	1984	C	133	19	14.29					
Mangal(22)	Rajasthan	Urban	< 10 yrs		1985-86	C	189	0	0					
Gupta(23)	Himachal Pradesh	Rural	<15 yrs	Yes	1986	C	217	11	5.06					
Narain(24)	Uttar Pradesh	Rural	All ages	Yes	1986	C	771	54	7	23.07	11.47	5.52	0	
Satpathy(25)	West Bengal	Rural	All ages	Yes	1986	C	581	1	0.17					
Risbud(26)	Maharashtra	Rural	< 10 yrs	Yes	1991	C	48	15	31.25	37.5	33.33	0		
Risbud(26)	Maharashtra	Rural	< 10 yrs	Yes	1992	C	128	20	15.63	33.33	13.04	6.67		
Thakur(27)	Chandigarh	Urban	All ages	Yes	1998-99	C	283	0	0					
John(28)	Tamil Nadu	Rural	< 10 yrs	Yes	1999	C	70	2	2.86					
Ray(29)	West Bengal	Urban	< 5 yrs		2000	C	290	0	0					
Sharma(30)	Chandigarh	Urban	< 14 yrs	Yes	2003	C	58	0	0					
Gupta(23)	Himachal Pradesh	Rural	<15 yrs	Yes	2004	C	69	0	0					
Mishra(32)	Madhya Pradesh	Rural	Children	Yes	2004	C	1204	14	1.16					
John(28)	Tamil Nadu	Rural	< 19 yrs	Yes	2006	C	59	0	0					

** P = Prospective; C = Cross-sectional.*

Measles CFR in India appears to have decreased during 1975-2008. We hypothesize that increased measles vaccination coverage in India is the main factor contributing to this decline, in addition to other factors including the introduction of vitamin A in case management and increasing vitamin A supplementation coverage. However, it may not be appropriate to generalize from this review that CFR has decreased for the entire population of India, since published data are only available for select communities in 12 Indian states or Union territories. In addition, 38% of all districts in India still had measles vaccine coverage less than 50% in 2005 and these districts are not proportionally represented in this review(33).

Widespread measles vaccination increases the average age of measles infection at the population level by decreasing the force of infection(34). Data from the US Centers for Disease Control and the recent WHO measles CFR review suggest that children <5 yrs infected with measles have increased mortality in comparison to children infected at an older age(2,5). Due to the small number of Indian CFR studies reporting the age of study participants, we were not able to statistically test differences between age groups. Nevertheless, a visual analysis of the Indian data in ***Fig.* 2** suggests that measles CFR is decreased in children >5 years.

A single dose measles vaccine is estimated to be 85% efficacious in preventing measles disease, and as a result a proportion of the total measles cases occurring in a community are expected to have been previously vaccinated(35). The proportion of total measles cases previously vaccinated in a community is anticipated to increase as vaccine coverage increases(36). For example, if measles vaccine coverage for a population is 50%, 13% of the total measles cases are expected to have been previously vaccinated. Whereas, if vaccination coverage is 90%, 57% of the total measles cases are expected to have been previously vaccinated. Multiple observational studies have found decreased measles mortality or measles complications in the previously vacci-nated(2,37-39).There is clear evidence of partial immunity in some studies, but confounding by differential access to health care could be a factor in some studies. When measles vaccination coverage increases, the expected proportion of total cases previously vaccinated increases, and in turn, the population case fatality ratio likely decreases.

Vitamin A deficiency is a known risk factor for measles mortality(40). Since 1987, the WHO and UNICEF have recommended vitamin A treatment of children with measles(41). A meta-analysis of randomized controlled trials found 200,000 IU of vitamin A given for 2 days was associated with a 64% reduction in overall mortality(42). Neverthe-less, measles case management with vitamin A may not have considerably affected Indian CFRs at the population level, since coverage of vitamin A treatment has been shown to be low in multiple

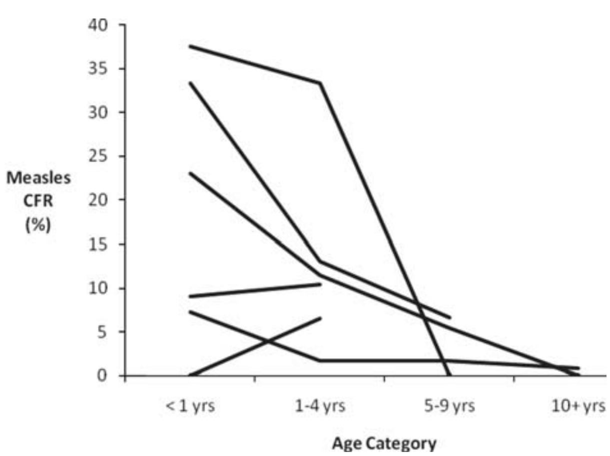

FIG.1 *Measles case fatality ratio by age category.*

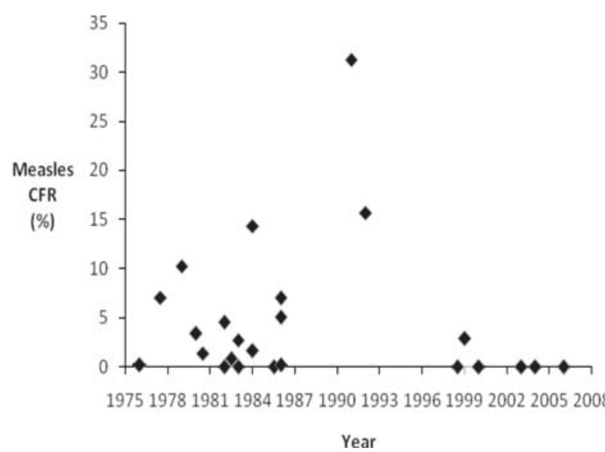

FIG.2 *Measles case fatality ratio by year of study (Studies with multiple years of follow-up are plotted at study midpoint).*

communities with high levels of measles transmission. A recent observational study in Madhya Pradesh found that only 15.8% of measles cases received therapeutic doses of vitamin A and another study conducted in slum areas of Kolkata found only 8.6% were treated(19,32). Routine vitamin A supplementation is also thought to decrease measles case fatality; however, the data suggest supplementation may not be as effective in preventing measles mortality as vitamin A administration at the onset of measles(43). Coverage of vitamin A supplementation may also be low in high risk populations. In a recent study in the slums of Delhi, only 37.6% percent of children 12-23 received a vitamin A supplement(44). Vitamin A treatment and routine supplementation have likely contributed to declining CFRs in India, but due to low coverage in communities at high risk for measles disease and mortality, the impact on population CFRs may not be considerable.

The data also suggest higher CFRs in rural areas compared to urban communities. This difference may be attributable to differences in access to health care and vaccination services. No significant differences were found by study design or for studies conducted in outbreak *vs.* endemic settings. These findings are similar to the results of the WHO case fatality review(5).

Overall, this review suggests measles CFR may be declining in India over time. We theorize that increased measles vaccination coverage is the main contributor to the decline. The impact of increasing vaccination coverage on measles mortality is greater than that expected from prevention of measles disease alone; since at higher coverage levels, the average age of infection is older and a larger proportion of measles cases are expected to have been previously vaccinated. Vitamin A treatment and supplementation decrease an individual's risk of measles mortality, but the impact in India at the population level may be minimal due to low coverage. In order to continue to decrease measles CFR in India; measles vaccination, vitamin A treatment, and routine vitamin A supplementation coverage should be increased. In addition, the cost effective strategy of introducing supplementary immunization activities to provide children with two doses of measles vaccine as well as increase single dose coverage could also significantly decrease mortality(45). India has greatly reduced the total number of measles cases and deaths over the past few decades, yet much more needs to be done to decrease the substantial burden of this preventable disease.

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