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Estimates of measles case fatality ratios: a comprehensive review of community-based studies†

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Background Global deaths from measles have decreased notably in past decades, due to both increases in immunization rates and decreases in measles case fatality ratios (CFRs). While some aspects of the reduction in measles mortality can be monitored through increases in immunization coverage, estimating the level of measles deaths (in absolute terms) is problematic, particularly since incidence-based methods of estimation rely on accurate measures of measles CFRs. These ratios vary widely by geographic and epidemiologic context and even within the same community from year-to-year.

Methods To understand better the variations in CFRs, we reviewed community-based studies published between 1980 and 2008 reporting age-specific measles CFRs.

Results The results of the search consistently document that measles CFRs are highest in unvaccinated children under age 5 years; in outbreaks; the lowest CFRs occur in vaccinated children regardless of setting. The broad range of case and death definitions, study populations and geography highlight the complexities in extrapolating results for global public health planning.

Conclusions Values for measles CFRs remain imprecise, resulting in continued uncertainty about the actual toll measles exacts.

Keywords Measles, community-based studies, case fatality ratio, mortality, review

Introduction

Although global deaths from measles have decreased markedly in past decades, largely as a result of intensive vaccination efforts,[1] estimating the magnitude of measles deaths is problematic. Measles case fatality ratios (CFR) vary widely by geographic and epidemiologic context and within the same community from year-to-year. Current estimates of CFRs used by the World Health Organization (WHO) in low-income countries range between 0.05% and 6%.[1,2] In complex emergencies or isolated areas where there is either low natural immunity or low vaccination coverage, the CFR is often between 10% and 30%.[3] Little research has explored the epidemiologic data to

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support these estimates and few comprehensive studies are reported in the published literature.

As part of the WHO response to the need for more in-depth information, we reviewed published community studies conducted between 1980 and 2008 reporting age-specific measles CFRs. This effort adds to those of others who have examined the global burden of measles,[1,2,4] but specifically addresses measles-specific mortality. Our goal was to review the available data from community studies on estimates of measles case fatality. We also identified information gaps and recommend what studies would help improve our understanding of the burden of measles and the impact of control measures.

Methods

Search strategy and selection criteria

We searched PubMed/MEDLINE for literature published either in English or with an English abstract in a foreign language publication. Combinations of the following groups of keywords were used: mortality, case fatality ratio or rate, community study and measles. References in published papers were also reviewed and used to identify other relevant publications. To avoid inclusion of duplicate studies, publications from the same region were cross-referenced considering the place and time period of reported studies.

Only papers published between 1 January 1980 and 1 July 2008, which reported on community-based studies conducted between 1974 and 2007 were included. Community in this context is used to indicate all cases within the specified population, regardless of where they were identified (i.e. home, health facility or hospitalized). National studies were included if the data reported were sufficient to meet the inclusion criteria described below. We excluded hospital-based studies as they may represent a biased sample and not reflect the severity of measles within the community.[5] We also excluded studies reporting on measles outbreaks in refugee or internally displaced persons camps as these studies report on specific and unique circumstances. Similarly, we excluded studies from industrialized countries with sustained high measles immunization coverage between 1990 and 2008.[6]

We defined a study as a unique analysis of measles or measles-related CFRs as defined by the authors. Studies were included if data could be extracted for two out of three of the following: (i) number of cases; (ii) number of deaths; and (iii) CFR. We extracted information on: the country where the study was conducted, the study site (urban/rural/both), the year the study began and the year the study ended, study mid-year, the length of the study, the type of the study (survey, review or outbreak investigation), measles case definition and the definition of a measles or measles-associated death, as well as on associated risk factors as reported by the study authors.

As available, the number of measles cases and deaths in each study was tallied for the following age-groups: 0–11 months, 12–23 months, 24–35 months, 36–47 months, 48–59 months, 60–119 months and >120 months. The study sample size was taken to be the number of measles cases investigated.

Review

First, we provide a descriptive analysis of the studies by location and study type and review the case definition, definition of a measles death and case ascertainment. Second, we explore potential differences in CFR by study type and setting, studies reporting no fatalities and studies reporting very high case fatality (above 15%). We also examined whether studies addressed potential risk factors for mortality. These factors included age of infection, secondary vs primary exposure, infection with complications, immunization status, gender, vitamin A administration and nutritional status. The roles of these factors, the natural history of measles and general epidemiologic characteristics have been reviewed elsewhere.[7–9]

A Kruskal–Wallis test was performed to evaluate differences in CFR by categories ($P < 0.05$ for chi-squared with no ties). Results for differences in age classes in CFR are presented as a notched box plot. In a notched box plot, the notches represent a robust estimate of the uncertainty about the medians for box-to-box comparison. The centre of the notched box plot is the median, and the endpoints of the notches are located at the median confidence intervals. The extreme endpoints of the notched box plot represent the 25% (lower) and the 75% (upper) quartiles of the data. When boxes have 'devil's ears' the confidence intervals surpass the inter-quartile range. Boxes whose notches do not overlap indicate that the medians of the two groups differ at the 5% significance level[10]).

When information was too inconsistently reported to perform statistical analyses, no results are presented. All analyses were performed using R statistical package R 2.4.0© (The R Project of Statistical Computing, 2008).

Results

In total, 58 publications were identified, providing 102 different measles studies with sufficient data in 29 countries.[11–68] Table 1 details the included studies grouped by country and WHO region. One publication covers 11 countries[11] and includes 18 different studies. Ten other publications include multiple studies: 2 studies in Guinea-Bissau,[68] Mozambique,[66] Gambia,[34] India,[46] Senegal,[69] Sri Lanka[44] and Sudan;[56] 3 studies in Niger, Chad and Nigeria;[53] 5 and 15 studies in India.[48,49]

The time period during which these studies took place is biased towards the beginning of the period investigated, with an average study midpoint of 1988.9 (median 1986). The majority occurred in

Table 1 Studies by region

WHO sub region	Country	Site	Year study started	Study length (years)	Reference	Type[a]	Total cases	CFR (age in months)							
								>11	12–23	24–35	36–47	48–59	60 +	Other age	Overall
AfrD	Burkina Faso	Urban	2000	1	Kambiré *et al.*[65]	S	2975	2.3	3.6	3.6	3.6	3.6	0.9 (60–179)	0.7 (180+)	1.50
AfrD	Chad	Urban	1993	0.8	Ndikuyeze *et al.*[41]	O	824	5.77	8.56	8.89	5.69	4.76			6.73
AfrD	Chad	Urban	2004	0.5	Grais *et al.*[53]	O	706	6.8	4.7	4.7	1.8	1.8	0.5		2.80
AfrD	Gambia	Rural	1981	0.9	Hull[35]	O	135	14.81 (0–131)	14.81 (0–131)	14.81 (0–131)	14.81 (0–131)	14.81 (0–131)	14.81 (0–131)	14.81 (0–131)	14.81
AfrD	Gambia	Rural	1981	0	Hull[34]	R	146	13.7 (0–131)	13.7 (0–131)	13.7 (0–131)	13.7 (0–131)	13.7 (0–131)	13.7 (0–131)	13.7 (0–131)	13.70
AfrD	Gambia	Rural	1981	0.9	Hull[35]	O	77	63.64	16.67	16.67	16.67	16.67	16.67		40.16
AfrD	Gambia	Rural	1983	1	Aaby[11]	R	132	9.09	9.09	9.09	9.09	9.09			9.09
AfrD	Gambia	Rural	1984	0.3	Lamb[36]	O	54	0					0		0.00
AfrD	Gambia	Rural	1988	1	Aaby[11]	R	54	0					0		0.00
AfrD	Ghana	Rural	1989	1	Dollimore[30]	S	961	21.37	22.86	19.87	19.31	9.33	7.79		16.76
AfrD	Ghana	All	1996	5	Bosu *et al.*[64]	S	1508	1.2	1.2	1.2	1.2	1.2	0.4		0.90
AfrD	Guinea-Bissau	All	1979	6	Aaby *et al.*[13]	S	459	27.85	25.56	24.36	9.17	9.17	4.0 (60–119)	28 (120+)	23.79
AfrD	Guinea-Bissau	Rural	1979	2.8	Aaby *et al.*[14]	S	162	46.67	52.38	26.92	40	5.26	4.55	11.76	26.79
AfrD	Guinea-Bissau	Rural	1984	1	Aaby[11]	R	162	33.66	33.66	33.66	33.66	33.66	8.2		20.93
AfrD	Guinea-Bissau	Urban	1980	1	Aaby *et al.*[15]	S	178	20.63	7.41	7.41	11.11	11.11	8.82		11.99
AfrD	Guinea-Bissau	Urban	1984	3	Aaby *et al.*[16]	S	90	11.11	11.11						11.11
AfrD	Guinea-Bissau	Urban	1988	1	Aaby[11]	O	161	15.32	15.32	15.32	15.32	15.32	10.81		13.07
AfrD	Guinea-Bissau	Urban	2003	0.75	Martins *et al.*[68]	S	8	0 (4–15)							0.00
AfrD	Guinea-Bissau	Urban	2003	0.75	Martins *et al.*[68]	S	77	0.1 (4–15)							0.09
AfrD	Niger	Rural	1991	0.7	WER[42]	O	528	24.88	24.88	24.88	8.89	8.89	8.89		16.89
AfrD	Niger	Urban	1991	0.1	Malfait *et al.*[37]	O	258	6.59	6.59	6.59	6.59	6.59			6.59
AfrD	Niger	Rural	2003	0.4	Nandy *et al.*[54]	O	945	15.7	11.5	11.5	11.5	11.5	4.9		9.74
AfrD	Niger	Urban	2003	0.5	Grais *et al.*[53]	O	767	7.2	4.2	4.2	3.9	3.9	0.7		3.90
AfrD	Nigeria	Urban	1992	1	Byass *et al.*[22]	O	481	4.72	4.72	2.82	2.82	2.82			7.54
AfrD	Nigeria	Rural	2004	0.5	Grais *et al.*[53]	O	1142	10.6	12.8	12.8	8.5	8.5	2.3		7.00
AfrD	Senegal	Rural	1982	1	Aaby[11]	R	160	26.88	26.88	26.88	26.88	26.88	26.88		26.88
AfrD	Senegal	Rural	1986	1	Aaby[11]	R	537	18.06	18.06	18.06	18.06	18.06	18.06		18.06
AfrD	Senegal	Rural	1991	4	Aaby *et al.*[12]	R	624	5.52	1.41	1.41	0		0	0	3.47

AfrD	Senegal	Rural	1994	0.8	Cisse *et al.*[27]	O	209	0	0	0	0	0	0	0.00
AfrD	Senegal	Rural	1983	3.8	Garenne and Aaby[32]	S	1466	11.52	10.86	13.62	7.36	2.53	1.23 (to 119)	0.0 (120+)	7.85
AfrD	Senegal	Rural	1985	1	Pison and Bonneuil[33]	O	56	24.1	24.1	24.1	13.33	13.33		0(60–131)	18.72
AfrD	Senegal	Rural	1987	3.5	Samb *et al.*[69]	S	630	2.33	5.75		0	0	1.2	0.54	1.96
AfrD	Senegal	Rural	1983	3.8	Samb *et al.*[69]	S	1500	12	12		0		1	0	6.50
AfrD	Sudan	Urban	1997	0.4	Ibrahim *et al.*[55]	S	95								9.47
AfrD	Sudan	All	2003	0.5	Coronado *et al.*[56]	S	523	0	0.7	0.7	0.7	0.7	0.003		0.40
AfrD	Sudan	Rural	2003	0.5	Coronado *et al.*[56]	S	621	4.17	1.92	1.92	1.92	1.92	0.006		1.30
AfrD Overall							19411							7.09	
AfrE	Burundi	Rural	1988	1.25	Chen *et al.*[24]	S	457	7.58	7.58	2.7	2.7	2.7			5.14
AfrE	DR Congo	Urban	1981	1	Aaby[11]	R	1069	5.99	5.99	5.99	5.99	5.99			5.99
AfrE	Ethiopia	Urban	1981	1	Aaby[11]	R	63	26.98	26.98	26.98	26.98	26.98			26.98
AfrE	Kenya	Rural	1985	2.16	Burstom *et al.*[21]	S	139	41.38	7.14	16.67	12.5	0	2.94 (60–119)	0.0 (120+)	11.52
AfrE	Kenya	Rural	1987	1	Burstom *et al.*[20]	S	252	29.27	46.15	46.15	47.5	47.5	2.94 (60–119)	0.0 (120+)	25.17
AfrE	Malawi	All	1996	2	Yamaguchi *et al.* [51]	S	542	0.93	2.76 (12+)	2.76 (12+)	2.76 (12+)	2.76 (12+)	2.76 (12+)		1.85
AfrE	Mozambique	Urban	1993	2	Cliff *et al.*[66]	S	2363								1.39
AfrE	Mozambique	Urban	1998	2	Cliff *et al.*[66]	S	2720								0.147059
AfrE	South Africa	Rural	1980	18	Uzicanin *et al.*[57]	S	10371							0.973869	
AfrE	Zambia	Urban	1982	1	Aaby[11]	R	316	1.9	1.9	1.9	1.9	1.9			1.9
AfrE	Zimbabwe	Urban	1980	10	Marufu *et al.*[38]	S	637	12.62	13.98	0.65			0.35		6.9
AfrE Overall							18929							2.02	
AmrD	Peru	Rural	1993	1	Sniadack *et al.*[50]	O	150	18.75	20						3.33
AmrD Overall							150								3.33
EmrD	Pakistan	Rural	1990	0.16	Murray and Rasmussen[39]	O	104	2.88 (0–167)	2.88 (0–167)	2.88 (0–167)	2.88 (0–167)	2.88 (0–167)	2.88 (0–167)	2.88 (0–167)	2.88
EmrD	Somalia	Rural	1980	1	Aaby[11]	R	600	2	2	2	2	2	2		2
EmrD Overall							704								2.13
SearB	Sri Lanka	All	1983	1	WER[44]	S	2386	1.09	1.09	1.09	1.09	1.09	1.09		1.09
SearB	Sri Lanka	All	1982	1.24	WER[44]	S	630	1.17	1.17	1.17	1.17	1.17			1.17
SearB	Sri Lanka	All	1999	2	Puvimanasinghe *et al.*[58]	O	4611								0.1
SearB	Thailand	Rural	1984	0.16	WER[43]	O	47	33.33	33.33	33.33	33.33	33.33	18.75 (60–119)	14.29 (120+)	22.12

(continued)

Table 1 Continued

WHO sub region	Country	Site	Year study started	Study length (years)	Reference	Type[a]	Total cases	CFR (age in months) >11	12–23	24–35	36–47	48–59	60 +	Other age	Overall
SearB	Overall						7674								0.64
SearD	Bangladesh	Urban	1983	1	WER[45]	S	3026	2.25	2.13	1.8	1.42	1.95	0.39 (60–71)	0.60 (72+)	1.51
SearD	Bangladesh	Rural	1980	0.5	Shahid *et al.*[47]	S	72	1.3 (0–23)							1.3
SearD	Bangladesh	Rural	1980	8	Fauveau *et al.*[31]	S	3514	3.06	2.66	1.9	1.51	0.52	0.37		1.67
SearD	Bangladesh	Rural	1980	1	Bhuiya *et al.*[19]	S	3458	1.26	2.22	1.66	1.66	1.66			1.71
SearD	Bangladesh	Rural	1981	1	Aaby[11]	R	510	3.92 (0–59)	3.92 (0–59)	3.92 (0–59)	3.92 (0–59)	3.92 (0–59)	4.15		3.92
SearD	Bangladesh	Rural	1989	2	DeFrancisco A *et al.*[28]	S	2775	1.65	0.83	0.96	0.96	0.96			1.15
SearD	India	Rural	1974	13	Chand *et al.*[23]	S	411	7.27	1.69			0.83 (48–179)	0.83 (48–179)	0.83 (48–179)	3.26
SearD	India	Rural	1979	0.9	Cherian *et al.*[25]	O	78	9.09	27.27	16	0	0			10.47
SearD	India	Rural	1980	1	Singh *et al.*[49]	R	266								3.38
SearD	India	Rural	1980	3	Dhanoa and Cowan[29]	S	372	3.76	3.76						3.76
SearD	India	Rural	1980	1	Singh *et al.*[49]	R	55								12.73
SearD	India	Rural	1980	1	Aaby[11]	R	50	18							18
SearD	India	Rural	1982	1	Singh *et al.*[49]	R	113	0.0 (0–119)	0.0 (0–119)	0.0 (0–119)	0.0 (0–119)	0.0 (0–119)	0.0 (0–119)	0.0 (0–119)	0
SearD	India	Rural	1982	1	Aaby[11]	R	78	3.85	3.85	3.85	3.85	3.85			3.85
SearD	India	Rural	1982	1	Singh *et al.*[49]	R	102	3.92	3.92	3.92	3.92	3.92			3.92
SearD	India	Rural	1983	1	Singh *et al.*[49]	R	132	0	0	0	0	0			0
SearD	India	Rural	1983	1	Singh *et al.*[49]	R	241	0	0	0	0	0	0.83		0.83
SearD	India	Rural	1983	0.41	Bhatia *et al.*[18]	O	515	2.72 (0–179)	2.72 (0–179)	2.72 (0–179)	2.72 (0–179)	2.72 (0–179)	2.72 (0–179)	2.72 (0–179)	2.72
SearD	India	Rural	1984	1	Singh *et al.*[49]	R	430	1.63	1.63	1.63	1.63	1.63			1.63
SearD	India	Rural	1984	1	Aaby[11]	R	78	10.26	10.26	10.26	10.26	10.26			10.26
SearD	India	Rural	1984	1	Singh *et al.*[49]	R	133	14.29 (0–179)	14.29 (0–179)	14.29 (0–179)	14.29 (0–179)	14.29 (0–179)	14.29 (0–179)	14.29 (0–179)	14.29
SearD	India	Rural	1985	1	Singh *et al.*[49]	R	2218	3.11 (0–179)	3.11 (0–179)	3.11 (0–179)	3.11 (0–179)	3.11 (0–179)	3.11 (0–179)	3.11 (0–179)	3.11
SearD	India	Rural	1985	1	Singh *et al.*[49]	R	46		23.92 (12–71)	23.92 (12–71)	23.92 (12–71)	23.92 (12–71)	23.92 (12–71)	23.92 (12–71)	23.92

SearD	India	Rural	1986	0.5	Narain *et al.*[40]	O	761	23.08	11.47	11.47	11.47	11.47	5.52 (60–119)	2.03 (120–179)	10.53
SearD	India	Rural	1986	1	Aaby[11]	R	79	5.06	5.06	5.06	5.06	5.06	0.0 (60+)		5.06
SearD	India	Rural	1986	1	Singh *et al.*[49]	R	581	0.17 (0–179)	0.17 (0–179)	0.17 (0–179)	0.17 (0–179)	0.17 (0–179)	0.17 (0–179)	0.17 (0–179)	0.17
SearD	India	Rural	1986	1	Singh *et al.*[49]	R	217	5.07 (0–179)	5.07 (0–179)	5.07 (0–179)	5.07 (0–179)	5.07 (0–179)	5.07 (0–179)	5.07 (0–179)	5.07
SearD	India	Rural	1991	0.16	Risbud *et al.*[46]	O	48	37.5	36.36	30.77	25	50	0	0	29.94
SearD	India	Rural	1992	1	Singh *et al.*[48]	O	14 522								4.1
SearD	India	Rural	1992	1	Singh *et al.*[49]	R	93	8.6 (0–179)	8.6 (0–179)	8.6 (0–179)	8.6 (0–179)	8.6 (0–179)	8.6 (0–179)	8.6 (0–179)	8.6
SearD	India	Rural	1992	1	Risbud *et al.*[46]	O	128	33.33	30	3.7	8.7	0	10.0 (60–71)	0 (72–119)	12.57
SearD	India	Rural	1993	1	Singh *et al.*[48]	O	6392								2.39
SearD	India	Rural	1994	1	Singh *et al.*[48]	O	10 561								2.4
SearD	India	Rural	1995	1	Singh *et al.*[48]	O	1931								3.68
SearD	India	Rural	1996	1	Singh *et al.*[48]	O	6922								4.1
SearD	India	Urban	1980	2	Singh *et al.*[49]	R	731	1.37 (0–179)	1.37 (0–179)	1.37 (0–179)	1.37 (0–179)	1.37 (0–179)	1.37 (0–179)	1.37 (0–179)	1.37
SearD	India	Urban	1985	2	Singh *et al.*[49]	R	189	0 (0–119)	0 (0–119)	0 (0–119)	0 (0–119)	0 (0–119)	0 (0–119)	0 (0–119)	0
SearD	India	Urban	2003	0.30	Sharma *et al.*[59]	O	58								0
SearD	India	Urban	2003	0.1	Ratho *et al.*[60]	O	12								16.7
SearD	India	All	1999	0.1	Thakur *et al.*[62]	S	283								
SearD	India	Urban	1999	0.03	Ray *et al.*[63]	S	5038								
SearD	Myanmar	Rural	1983	1	Chin and Thanung[26]	S	166	0	13.75	13.75	13.75	13.75	4.0 (60–119)		8.88
SearD	Myanmar	Rural	1985	1	Aaby[11]	R	182	4.4	4.4	4.4	4.4	4.4	12.09 (60+)		8.05
SearD	Myanmar	Rural	1985	1	Aaby[11]	R	1340	3.05	3.05	3.05	3.05	3.05	0.54 (60+)		1.8
WprA Overall							68 907								2.86
WrpB	Calmbodia	Rural	2000	2	Oum *et al.*[61]	S	228								1.8
WrpB	Marshall Islands	Rural	1982	1	Aaby[11]	R	340	11.5	11.5	11.5	11.5	11.5	0		11.5
WrpB	Marshall Islands	All	2003	0.33	Hyde *et al.*[67]	O	821	0	0.68	0.68	0.68	0.68	0	0	0.4
WprB	Phillipines	Rural	1983	1	Almoiradie–Javonillo and Javonillo[17]	O	126	6.35 (0–179)	6.35 (0–179)	6.35 (0–179)	6.35 (0–179)	6.35 (0–179)	6.35 (0–179)	6.35 (0–179)	6.25
WprB Overall							1515								3.56

[a]S, survey; O, outbreak; R, review.

India (34.31%),[11,18,23,25,29,40,46,48,49,59,60,62,63] Senegal (7.84%)[11,12,27,32,33,69] and Guinea-Bissau (7.84%).[11,13–16,68] Six studies each took place in Bangladesh[11,19,28,31,45,47] and Gambia;[11,34–36] four in Niger;[37,42,53,54] and three studies in Myanmar (Burma),[11,26] Sri-Lanka[44,58] and Sudan.[55,56] Chad,[41,53] Ghana,[30,64] Kenya,[20,21] Marshall Islands,[11,67] Mozambique[66] and Nigeria[22,53] had two studies each. One study each took place in Burkina-Faso,[65] Burundi,[24] Cambodia,[61] DR Congo (ex-Zaire),[11] Ethiopia,[11] Malawi,[51] Pakistan,[39] Peru,[50] Philippines,[17] Somalia,[11] South Africa,[57] Thailand,[43] Zambia[11] and Zimbabwe.[38]

The vast majority of studies were conducted in rural areas (67.65%) with 42.0% of these ($n = 29$) in India. Of the remaining studies, eight were nationally representative [Ghana (1), Guinea-Bissau (1), India (1), Malawi (1), Marshall Islands (1) and Sri Lanka (3)]. Twenty-five (24.51%) of the studies were carried out in urban areas, of which five were conducted in urban areas of India and Guinea-Bissau, two urban studies in Chad, Mozambique, Niger and Sudan and one each in Bangladesh, Burkina Faso, DR-Congo (ex-Zaire), Ethiopia, Nigeria, Zambia and Zimbabwe.

When examining studies by type, 38.24% ($n = 39$) were retrospective reviews (mainly of surveillance data from health centres), 31.37% ($n = 32$) were outbreak investigations and 30.39% ($n = 31$) were surveys (mainly community based—i.e. household surveys).

Case definition and definition of a measles death

Thirty-seven studies used the WHO clinical case definition for measles defined as any person in whom a clinician suspects measles infection, or any person with fever and maculopapular rash (i.e. non-vesicular) and cough, coryza or conjunctivitis. Of these, laboratory confirmation for a subset of cases was available in only 14. Eight studies used parental reporting to define measles cases. The majority of studies ($n = 49$) did not explicitly define a measles case. The remaining studies use surveillance data collected from local health district authorities but some do not cite a specific case definition.

Seventeen studies provided a definition of measles death with most considering a measles death to be any death within 6 weeks (45 days) of rash onset excluding accidental deaths. Three studies used a 30 day limit,[53,54,56] whereas another considered 60 days;[63] all four excluded accidental deaths. Two studies employed a more restrictive definition including deaths that occurred within 45 days of rash onset with diarrhoea, dysentery and/or respiratory problems.[19,28] One study included cases where measles was listed either on the death certificate or clinical signs within 3 months of death from a parental interview.[26] One study considered a measles death to be any death that occurred after a measles complication (diarrhoea, pneumonia, otitis media, encephalitis or haemorrhagic rash).[55] One study restricted measles deaths to those within 15 days of onset of rash.[37] Two others stated that only acute deaths from measles were considered from death records where measles is presumably listed as the primary cause of death[38,51] and one used only verbal autopsy.[61] One study exploring the longitudinal impact of measles infection used a wide definition, including cases that died up to 3 years after infection.[12]

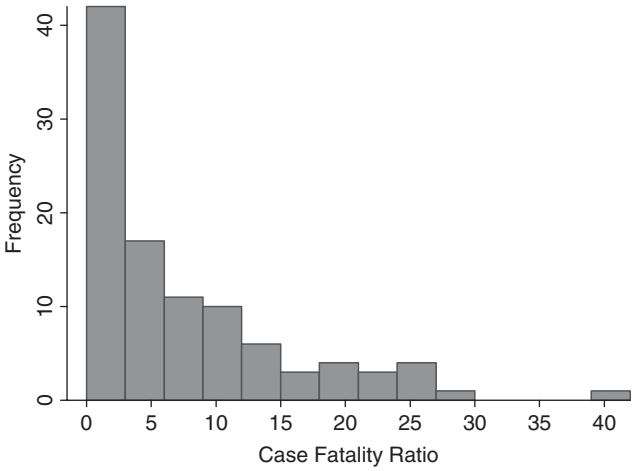

Figure 1 Histogram of overall CFRs reported by all studies

Case ascertainment

Most studies used reported cases of measles from health centres or relied on parental recall. Previous studies in areas of high measles incidence have shown both parental and medical diagnoses to be highly reliable.[11,13,69] However, measles can be difficult to distinguish from other rash–fever illnesses like rubella, dengue, etc., especially in low incidence settings where physicians are less accustomed to seeing it.[28] Although several studies addressed the possibility of misclassification in either parental recall or surveillance data, quantification of this difference was not discussed. Two sets of studies used data from active demographic surveillance systems in Bangladesh and Senegal. One study aimed to assess antibody response 7 months after a measles epidemic and used laboratory data for measles virus haemagglutination-inhibition antibody for case ascertainment.[26]

Descriptive analysis

In total, 117 336 cases and 3857 deaths (overall CFR = 3.29) were included in the data set. The median CFR was 3.91 (mean = 7.40, range = 0–40.15). Figure 1 shows a histogram of the CFRs reported for all age-groups in the 102 studies. The sample size varied considerably with a median sample size of 328 measles cases (mean = 1150).

CFR by study type and setting

The median CFR for outbreak investigations was 5.18 (2.56, 11.55), for reviews 3.92 (1.39, 12.73) and for surveys 1.85 (1.17, 9.5). The minimum CFR for all study types was 0.0 and the maximum was 40.16 for outbreak investigations, 26.98 for reviews and 26.79 for surveys. Differences were not statistically significant ($P = 0.54$).

Although across all studies there was no difference in median CFR by study type, when we examined only studies in rural areas, a greater difference emerges (although not statistically significant, $P = 0.42$). For outbreak studies in rural areas only, the median CFR was 6.63 (2.88, 14.81). In reviews, the median CFR in rural areas was 5.06 (2.0, 12.73) and in surveys 3.51 (1.58, 8.88).

In studies that are nationally representative ($n = 8$), the median CFR was 1.0 (0.23, 1.51). In studies located in rural areas ($n = 69$), the median CFR was markedly higher, up to 5.06 (2.0, 12.57, $P = 0.001$), and also in urban areas ($n = 25$), where the median CFR was 2.8 (1.0, 7.54, $P = 0.07$).

Studies with no case fatalities

Ten studies reported no fatalities.[11,27,36,49,59,62,63,68] The studies with no case fatalities had low sample sizes (median = 122.5) but similarly low sample sizes were also seen in studies with very high CFRs (see next section). We note, however, that minimum sample sizes of 140 and 70 are, respectively, required for the probability to be >50% of observing a CFR >0 when the true CFR is 0.5 or 1.0. Two studies in rural Gambia and one study in Senegal occurred in highly immunized population.[11,27,36] A clinical trial conducted in Guineas-Bissau reported no deaths in the vaccinated group.[68] The seven remaining studies occurred in India where the lack of fatalities was attributed to adequate health care facilities for treatment of measles-associated complications.

Studies with very high CFR

Sixteen studies reported CFRs above 15.0 for all age-groups.[11,13,14,20,30,33,35,42,43,46,49,60] Sample sizes ranged from 12 to 961 measles cases (median = 118.5). The majority of very high CFR studies describe outbreaks in isolated populations. During an outbreak in Thailand, measles spread rapidly between two villages within walking distance of one another and cases ranged from 7 months to 25 years.[43] A similar epidemic occurred in a remote tribal population in Thane district, Maharashtra, India.[46] One study points out the high prevalence of malnutrition as a possible explanation for the elevated mortality.[60] In the remaining studies, vaccination coverage was extremely low or the study began before the advent of routine measles vaccination, regardless of study location.

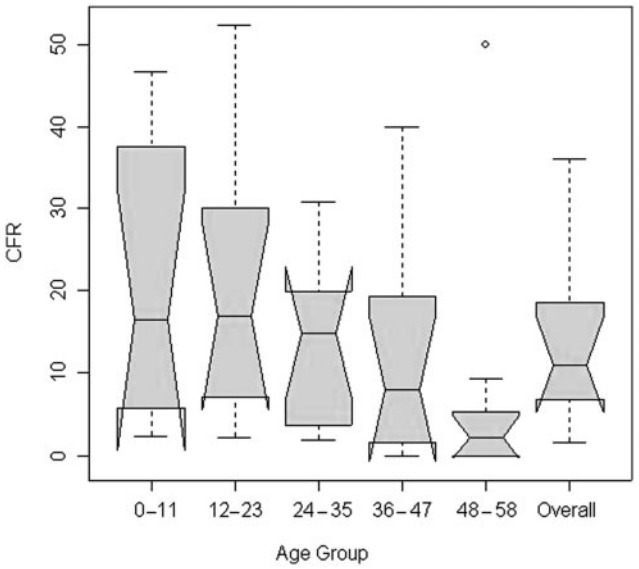

Figure 2 Notched box plot of CFR for studies with defined age groups. In a notched box plot, the notches represent a robust estimate of the uncertainty about the medians for box-to-box comparison. Boxes whose notches do not overlap indicate that the medians of the two groups differ at the 5% significance level. The median is represented by the horizontal line through each box

Risk factors

Age at infection

Across 28 studies reporting average age of infection, there was no clear direct relationship between CFR and age of infection or study location.[11,14,17,20,26,32,33,35,36,40,43,51,53–56,64,66] Of these, 10/28 occurred in settings where there was no measles immunization[11,20,26,32,35,36,51] where the average age at infection is known to be lower. One study in Senegal concluded that a major increase in measles vaccination coverage increased the average age of infection from 4 to 7 years. In the period before the increase in vaccination coverage, 12% of cases occurred in children under the age of 1 year compared with 2% after. Similarly, in the period before the increase in coverage 12% of cases were in children between 1 and 2 years, compared with 6% in the period after the increase in coverage. The increased age of infection was said to have accounted for a 20% decline in measles CFR.[69]

Few studies employed age groups refined enough to estimate CFR by single years of age for children under 5 years of age. Even fewer studies addressed case fatality in infants (age 0–11 months).[28,31,35,38,47] Of the studies ($n = 10$) that allowed for the analysis of CFRs for children under 5 years of age, the age-specific CFR varied considerably by age class but almost all exhibited a decreasing trend with each year increase in age. A slightly different pattern is seen, however, when the data are aggregated across studies (Figure 2),

particularly in comparing the CFR for children 0–11 months and 12–23 months. For ages 0–11 months the median CFR was 16.45 (0.59, 32.3); for age 12–23 months the median CFR was 16.86 (5.44, 28.28); for age 24–35 months the age-specific CFR was 14.81 (6.73, 22.89); for age 36–47 months the median CFR was 8.03 (−0.86, 16.92); and for age 48–59 months the median CFR was 2.24 (−0.39, 4.87). Differences between age groups were borderline $P = 0.052$).

Secondary vs primary case

Higher CFRs among secondary cases in several studies were attributed to a greater dose of measles virus and other infectious agents that secondary cases may have received from the index case.[11,19,20,32–37] The definition of secondary case used in these studies varied. Definition of a primary or secondary case was based within a household,[19,20] between a household and compound[27] or among family members.[37]

Infection with complications

Mortality was associated with diarrhoea and respiratory complications (including pneumonia) and otitis media and encephalitis in several studies.[11,18,20,21,23,26,31,38,40,44,47,51,53,54,58–60,62,63,67,68] Of the studies addressing the association between complications and death, respiratory complications were more directly associated with risk of death than diarrhoeal infections; nonetheless, one study found pneumonia more frequently among mild measles cases than among severe cases.[55]

Immunization status

The majority of studies suggest that children with a record of previous vaccination have a lower CFR and reduced complications.[11–16,20,22,35,36,41,48–50,56,57,69] Milder measles disease was also associated with a lower CFR in vaccinated children,[12–14,69] but other studies did not find any difference.[55] One study in Senegal suggested that the observed decrease in CFR could be due to the increase in measles vaccination coverage and the older age of the measles cases.[69] Two other studies examined the difference in CFR before and after supplemental immunization campaigns. Cliff *et al*.[66] analysed information from the routine surveillance system on total measles cases and deaths to compare pre- and post-supplemental vaccination campaigns in five urban areas of Mozambique. The CFR declined in Maputo, the capital city from 2.3% to 0.3% and one other urban area from 1.7% to no deaths; remained the same in two other cities; and increased in one area from no deaths to a CFR of 0.1% (one death reported). An additional study exploring measles incidence before and after a mass vaccination campaign in Burkina Faso found an overall CFR of 1.5% after the campaign, but the CFR pre-campaign is not reported.[65] CFR was higher among children aged 0–4 years, but 36% of deaths were documented among the age group that was not offered vaccination during the national campaign.

It is also likely that unimmunized children may be at higher risk for additional reasons, experiencing a higher CFR due to a lack of access to care or cultural beliefs,[18,23,26,40,53] poor underlying health status or below the age of vaccination.[18,28,31,37]

Sex

Some studies found no difference between sex and the occurrence of respiratory complications, diarrhoea and deaths.[38,53–55,58,64] Studies in Bangladesh, India and Nigeria found excess measles mortality in females.[19,23,31,53] Free diarrhoea treatment centres in Matlab, Bangladesh appear to be used less frequently for female children.[19] A slightly elevated adjusted odds ratio for female sex as a risk factor for mortality in urban Nigeria is also reported.[22]

Vitamin A deficiency

One study in Bangladesh (of 25 443 children aged 0–95 months) specifically aimed to measure the difference between measles acute case fatality and measles-associated fatalities and vitamin A supplementation, and no marked difference in acute measles fatality between vitamin A supplemented and placebo groups was found (15.4% vs 14.5%).[31] One study in Niger did not find either any relationship between the vitamin A supplementation and the probability of death.[54] Conversely, one study registered deaths only in those children that did not receive vitamin A supplementation.[56] In a review of longitudinal studies in Senegal, a reduction in post-measles infection mortality could not be related specifically to treatment with vitamin A.[12]

Malnutrition

A review of historical studies concluded that factors, such as overcrowding, the intensity of exposure and patterns of disease transmission are more important than nutritional status as risk factors for measles mortality.[9,11,13] In another review, the data were judged insufficient to establish an association between nutritional status before illness and mortality from measles.[48] In a small retrospective study in Bangladesh, no difference was found between cases and controls in weight-for-height and height-for-age markers for overall nutritional status; but only 1 of the 77 cases died, thereby making an assessment of the influence on mortality impossible.[47] One study in Sudan found higher risk of complicated measles in children who were underweight but not in those wasted or stunted.[55] In urban Nigeria, measles cases were more likely to be malnourished at the time of survey or death (13.9% compared with 6.5% of controls) but no information was provided on how malnutrition was measured.[22] Nutritional status had no effect on susceptibility or outcome in another study.[36] Two studies, one in Niger and one in India,

suggested the high prevalence of malnutrition as a plausible explanation for the high CFR.[54,60] Another study found that there may be an increased CFR for severely malnourished children (<60% weight by standard weight-for-height measurement), but severely malnourished children account for only a small proportion of measles deaths.[11]

Country and regional estimates of CFR

Although attempts were made to develop a model for deriving country-specific CFRs, most of the models were found to give implausible results. Even for countries with data identified in this review, the considerable degree of variation in these studies (Figure 3) precluded using these studies, or aggregates of these studies, as point estimates of measles CFR.

It is not possible to conclude with certainty that the CFR value derived in a given study reflects the real value for an entire district or country. Based on the findings of this review, an expert group was constituted to categorize countries by similarity of factors that influence CFR, and derived a set of CFR ranges among children aged 1–4 years, for use in determining the global burden of measles[1] (Table 2).

Discussion

To measure progress in measles mortality reduction, refined estimates of measles and measles-associated mortality are required. CFRs vary widely among countries, regions, age and within the same community in different years, making generalizations difficult. Even if a country or region has a reliable estimate for CFR, extrapolating this value to other years or regions can be problematic. The heterogeneity and sparseness of the available data mean that values for CFRs remain imprecise, resulting in an uncertainty about the actual toll measles exacts. Moreover, the sensitivity and specificity of definitions of measles cases and deaths reported may vary widely within and between studies and study groupings, such that aggregated analyses should be interpreted with caution.

Although our review included all published studies meeting the inclusion criteria, only 29 countries are represented in the data set and three countries, India, Senegal and Guinea-Bissau, are over represented, particularly with data drawn from demographic surveillance sites that may not be representative of the general population as these highly studied populations frequently tend to be well-vaccinated and have high access to care. Age groups, definitions of measles cases and deaths, reporting of complications and other risk factors, sample size and data

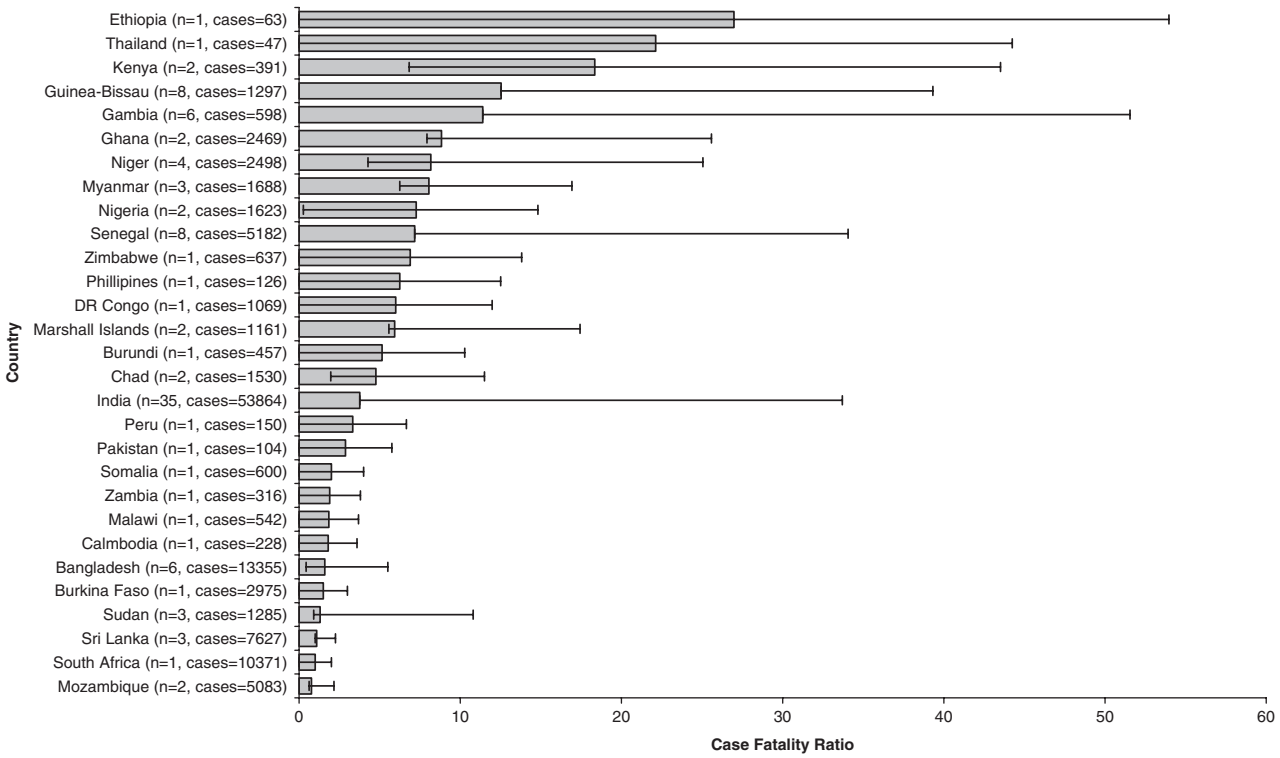

Figure 3 CFRs by country. The bar represents the median of all studies (n = number of studies in the country), with the lines representing the minimum and maximum of the studies from the country

Table 2 CFRS by region and level

CFR range (%)	AMR	EUR	WPR	SEAR	EMR	AFR
0.05	All	Developed economies	NZ, Australia, Japan			
0.1–0.5		Economies in transition	Malaysia, Rep Korea, Singapore, Brunei, China, Pacific Islands	DPRK, Thailand, Maldives	All others	Mauritius, Swaziland
0.5–1			Philippines, Mongolia	Bhutan, Sri Lanka	Jordan, Egypt, Iraq	
1–2				India, Bangladesh	Pakistan	
2–3			Cambodia, VietNam	Nepal, Indonesia, Timor-Leste	Djibouti, Yemen	Malawi, South Africa, Cape Verde, Algeria
3–4			Laos, PNG	Myanmar	Sudan	Angola, Ethiopia, Uganda, Kenya, Tanzania, Cameroon, Madagascar
4–5					Afghanistan, Somalia	Chad, Congo, Nigeria, Central African Republic, Equatorial Guinea, Gabon, Namibia, Sao Tome and Principe, Comoros, Mozambique, Côte d'Ivoire, Lesotho, Rwanda, Burundi, Zambia, Botswana, DR Congo, Niger, Senegal, Mali, Burkina Fase, Ghana, Eritrea
5–6						Sierra Leone, Guinea, Liberia, Togo, Guinea-Bissau, Mauritania, Benin, Zimbabwe, Gambia, Seychelles

AMR = American Region, EUR = European Region, WPR = Western Pacific Region, SEAR = South East Asian Region, EMR = Eastern Mediterranean Region, AFR = African Region.

analysis varied widely among the studies reviewed. This lack of uniformity presented barriers for data aggregation allowing only for the description of general trends and no further direct analyses.

Nevertheless, several overall conclusions about measles CFRs from these studies can be drawn. First, vaccination is associated with milder measles and lower CFRs in most studies providing information on vaccination status of measles cases. Second, patterns demonstrated in the studies included in this review suggest that higher CFRs occur in outbreaks; children under 5 years of age; in secondary cases; in cases with complications; and in unimmunized individuals. Although the studies in this review did not support a clear benefit of vitamin A supplementation on mortality, other evidence suggests the contrary and vitamin A supplementation is recommended by the WHO.[70,71]

This review also suggests that studies done in rural and urban areas alone exhibited statistically significant higher CFRs than studies covering an entire country, likely attributable to these studies having been done in areas of known high measles incidence, whereas country-wide studies cover areas of both low and high incidence.

As future studies are designed, it is important to consider what they should include to provide the maximum amount of information possible to better assess mortality. An ideal CFR study should first and foremost include the definition of a measles case using the standard WHO case definition. Laboratory confirmation of a small number of cases is preferable, but not always possible in low income settings. The definition of an acute measles death is any death, except accidents and trauma, taking place within 30 days of the onset of rash. Ideally, to truly measure the burden of measles, measles-associated deaths should be considered; that is, deaths of measles cases due to complications or outside of the acute measles period but within 3 months of rash onset. When measles-associated deaths are included in the analysis, the primary cause of death should also be noted. In studies employing death certificates from community health centres or hospitals, an estimation of the percentage of deaths occurring at home should also be reported where feasible.

A clear difficulty in obtaining better information on CFRs is ensuring an adequate sample size. In small outbreaks, the low sample size (number of cases investigated) leads to wide confidence intervals.

By increasing the number of cases investigated the confidence interval can be narrowed. Byass estimated the minimum sample size required for measles outbreak investigations to determine CFRs within reasonable limits.[5] Comparison of CFRs between age-groups requires larger numbers of measles cases to adequately assess age differentials.

When reporting results, studies should completely describe the type of data used to identify cases (i.e. routine surveillance, household survey) and specify the time period. Data from health centres should specify whether cases were confirmed by a health care worker or by a standardized case assessment form. Household surveys should specify whether an exhaustive or sample of households were assessed. If a sample of households was assessed, an overview of the sampling scheme should be provided along with the definition of household used in the study.[37] As in any epidemiologic study, the potential for bias or misclassification in ascertainment of cases and deaths should be considered. For ethical reasons, measles CFR studies must be retrospective by design as it would be unethical to study prospectively measles deaths and not intervene in the population to vaccinate unvaccinated children or to treat measles cases. See reference Byass[5] for further guidance on conducting CFR studies.

Refining estimates of measles CFRs would provide not only important information on the progress of measles mortality reduction initiatives and burden of disease, but also on the availability of adequate care. Because of the high visibility of measles as a childhood killer, measles CFR can be used as a marker of availability and utilization of primary health services.[7] Although current measles mortality reduction initiatives have made significant progress, further research on measles CFRs is essential to accurately measure levels of measles mortality, and particularly for estimating the contribution that measles mortality-reduction activities can make towards achieving the Millennium Development of reducing child mortality rates.[52]

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KEY MESSAGES

- Patterns demonstrated in the studies included in this review suggest that higher measles CFRs occur in outbreaks; in children under 5 years of age; in secondary cases; in cases with complications; and in unvaccinated individuals.
- Future studies on CFRs should include the standardized WHO case definition of measles; where possible, laboratory confirmation of a subset of cases; adequate sample sizes; and clear definitions of methods and data for case ascertainment and the time period covered.
- Future studies should also examine deaths associated with complications from measles within 3 months of disease onset, and not be limited to the acute period.
- Refining estimates of measles CFRs is important not only for quantifying global progress in reducing measles mortality, but also on understanding of the availability of adequate care for achieving the MDG goal of reducing child mortality rates.

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