Measles deaths in Nepal: estimating the national case–fatality ratio

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Objective To estimate the case–fatality ratio (CFR) for measles in Nepal, determine the role of risk factors, such as political instability, for measles mortality, and compare the use of a nationally representative sample of outbreaks versus routine surveillance or a localized study to establish the national CFR (nCFR).

Methods This was a retrospective study of measles cases and deaths in Nepal. Through two-stage random sampling, we selected 37 districts with selection probability proportional to the number of districts in each region, and then randomly selected within each district one outbreak among all those that had occurred between 1 March and 1 September 2004. Cases were identified by interviewing a member of each and every household and tracing contacts. Bivariate analyses were performed to assess the risk factors for a high CFR and determine the time from rash onset until death. Each factor's contribution to the CFR was determined through multivariate logistic regression. From the number of measles cases and deaths found in the study we calculated the total number of measles cases and deaths for all of Nepal during the study period and in 2004.

Findings We identified 4657 measles cases and 64 deaths in the study period and area. This yielded a total of about 82 000 cases and 900 deaths for all outbreaks in 2004 and a national CFR of 1.1% (95% confidence interval, CI: 0.5–2.3). CFR ranged from 0.1% in the eastern region to 3.4% in the mid-western region and was highest in politically insecure areas, in the Ganges plains and among cases < 5 years of age. Vitamin A treatment and measles immunization were protective. Most deaths occurred during the first week of illness.

Conclusion To our knowledge, this is the first CFR study based on a nationally representative sample of measles outbreaks. Routine surveillance and studies of a single outbreak may not yield an accurate nCFR. Increased fatalities associated with political insecurity are a challenge for health-care service delivery. The short period from disease onset to death and reduced mortality from treatment with vitamin A suggest the need for rapid, field-based treatment early in the outbreak.

Une traduction en français de ce résumé figure à la fin de l'article. *Al final del artículo se facilita una traducción al español.* الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Estimates of measles-related deaths are critical for monitoring progress towards global measles elimination goals and for prioritizing measles control in relation to other public health interventions. However, such estimates vary widely. WHO uses underlying case–fatality ratios (CFRs) to estimate measles-related deaths.[1,2] Studies of measles CFRs have generally been restricted to one or two areas within a country or to specific populations involving fewer than 1000 cases, and they have not evaluated geographic variability or the localized effects of factors such as political insecurity.[3–17] To our knowledge, no nationally representative study of measles CFRs has previously been conducted in a measles-endemic country.

Localized CFR estimates in south-east Asia[4,9–11,13,15,16] and globally[3,5–8,12,14,18–20] have varied from less than 1% to 25%, but many studies were conducted before implementation of the Integrated Management of Childhood Illness strategy and recommendations to administer vitamin A to all measles cases. Therefore, many of these studies may not reflect the current situation. No estimates of measles CFRs have previously been published from Nepal, a country characterized by geographic inaccessibility and, for the last decade, by political unrest. Uncertainty about the national case fatality ratio (nCFR) for measles hinders evaluation of the measles control programme, including strategies to reduce measles mortality.

This paper describes a study of measles cases and deaths in a nationally representative sample of measles outbreaks. The aim was to estimate the nCFR, establish a baseline for evaluating disease burden, and determine the role of political instability and other risk factors for measles mortality. We used the data to estimate the number of measles cases and deaths that occurred in Nepal in 2004. We also examined the implications of determining the nCFR using a nationally representative sample of outbreaks rather than data from routine surveillance or a localized study.

Methods

Setting

Nepal has a population of 28 million people, of whom 86% live in rural areas, 42% are unemployed and nearly 33% live in poverty.[21,22] The country is administratively divided into 75 districts in five development regions – far-western, mid-western, western, central and eastern. Topography

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divides Nepal into three ecological zones – the Himalayas in the north bordering China, the Ganges plains in the south bordering India and the Himalayan foothills in-between. These regions and zones vary with respect to economic status, accessibility and health infrastructure, with the western regions being less developed than the central and eastern regions. From 1996 to 2006, a Maoist insurgency led to more than 12 000 deaths and internal displacement of 400 000 rural families, and it destroyed physical infrastructure worth at least US$ 250 million.[23] Security concerns, lack of infrastructure and mountainous terrain make the delivery of public health services challenging in much of Nepal.

Measles is endemic in Nepal; an estimated average of 90 000 cases per year occurred from 1994 to 2002, based on extrapolations from routine surveillance reports.[24] Routine measles vaccination began in three districts in 1979 and was expanded nationwide by 1989; children receive a single dose of measles vaccine at 9 months of age. The most recent Demographic and Health Survey, conducted in 2001, estimated that coverage with one dose of measles vaccine among children aged 12–23 months was approximately 71% overall, with regional variability from 65% to 79%.[25]

Routine surveillance system

A measles outbreak is defined as more than five cases in a geographic area (i.e. village or urban ward) during a one-week period. Since 1994, Nepal's national Health Management Information System has received monthly data on such outbreaks from local heath personnel or other local authorities in 4000 clinics nationwide. Depending on available resources and severity, some of these outbreaks are then referred to district rapid response teams for investigation.

Nationally, 137 measles-like outbreaks were reported through the routine surveillance system during the study period – 1 March to 30 September 2004 – which corresponded to the peak season for measles. District rapid response teams investigated 106 (77%) of these outbreaks; serum samples were obtained from at least five patients per outbreak and tested by enzyme-linked immunosorbent assay (ELISA) for the detection of immunoglobulins against the measles and rubella viruses (Enzygnost Anti-measles Virus IgM and Enzygonst Anti-rubella Virus IgG, Dade Behring, Marburg, Germany). Testing was completed at the National Public Health Laboratory in Nepal, which is accredited by WHO and is part of the Global Measles Laboratory Network.[26] Of the investigated outbreaks, 92 (86.8%) were laboratory-confirmed for measles, 6 (5.7%) were confirmed for rubella and 8 (7.5%) were mixed.

Study design

In the first stage of this retrospective study of measles cases and deaths, we selected 37 districts by simple random sampling. The number of districts selected in a region was proportional to the number of districts in that region relative to all districts in Nepal. A study supervisor visited the district medical officer in each selected district and obtained the number of previously reported and unreported measles outbreaks from clinic registers that occurred during the study period. For the second stage of sampling, one outbreak in each district was selected randomly.

The study was approved by the institutional review board of the Institute of Medicine, Tribhuvan University, Nepal, and by the Department of Health Services, Ministry of Health, Nepal.

Data collection

Data were collected from September 2004 to January 2005. Each outbreak was investigated by a study team comprising two government health workers or enumerators from the outbreak area, and a supervisor with, at minimum, a degree in public heath or medical care. A separate survey team was formed for each of the 37 outbreaks because of language differences and distance between outbreaks. All teams in a region were overseen by a study coordinator. A data collection field guide was used to ensure uniform data collection. Investigators trained coordinators in survey methods, data collection, quality control, team coordination, ethical issues and supervision. Teams were trained in mapping, conducting house-to-house surveys, completing forms, obtaining informed consent and querying about deaths.

Survey teams first confirmed the presence of measles in at least five village residents based on clinical histories from caregivers. Enumerators then conducted a search for measles cases in every single house in the village. Dwellers were asked to identify household members who had had measles during the study period. Following written informed consent, either the case or the guardian of children too young to respond by themselves was interviewed in Nepali or the local language using the Nepali study questionnaire. To map the entire outbreak area, the survey team also searched for cases in all adjoining villages and wards.

Outcome measures and risk factors

A resident was any person, dead or alive, who had lived in the outbreak area for at least 12 months before the interview. A measles case was any resident who met the WHO measles case definition – history of fever and generalized maculopapular rash, and one or more of cough, coryza or conjunctivitis[27] – as reported by the case or case guardian. As per WHO guidelines, a measles death was defined as the death of a person with measles within 30 days of rash onset, unless the death was unrelated to the disease.[28] Dates of rash onset and death were reported by the interviewed case or case guardian using a local calendar; symptoms were reported in the local language with the assistance of field guides.

To determine the factors associated with measles morbidity and mortality, we evaluated the demographic characteristics and treatment history of the cases as reported by the case or case guardian. Ethnicity was determined based on family name, as is standard practice in Nepal. Measles vaccination status was evaluated by reviewing the patient's vaccination card or, in its absence, by querying the case or caregiver about his or her vaccination history. Less than 3% of the cases had a vaccination card.

Since 1998, the UN has categorized Nepal's districts by security phases, depending on the degree of safety and restricted movement of UN personnel.[29] We used these categories to classify districts from September 2002 to March 2004 as "moderately insecure" if they were designated as "phase I: warning" or "phase II: restricted" throughout the period; as "highly insecure" if they were

sometimes designated as "phase III: relocation"; and as "critically insecure" if they were consistently designated as "phase III: relocation".

Sample size

The required sample size was initially found to be 637 for a simple random sample of cases, an estimated 4% CFR (based on expert opinion and results from studies in the region), a 2% margin of error and a 0.95 confidence level. After adjustments for an anticipated design effect of 2, a 10% participation refusal rate, and a mean of 38 cases per outbreak (estimated by the Programme for Immunization Preventable Diseases, WHO, Nepal), the target sample size became 1401 cases in 37 outbreaks.

Data analysis

Data were double-entered using Epi Info 2002 (Centers for Disease Control and Prevention, Atlanta, GA, United States of America) and processed in SAS version 9 (SAS Institute, Cary, NC, USA); SUDAAN version 8.0 (Research Triangle Institute, Research Triangle Park, NC, USA) was used for all analyses. Bivariate analyses with percentage estimates and their 95% confidence intervals (CIs), as well as factor-level χ^2 tests were used to assess the risk factors for a high CFR and time from rash onset until death. Statistical significance was set at $P < 0.05$. To assess the simultaneous contribution of each factor to the nCFR, we constructed multivariate logistic regression models; the cases least likely to die in the bivariate analysis served as the reference group for each factor. To arrive at a final main-effects model of factors associated with a high measles CFR, we conducted backward elimination by removing variables in the model until all remaining factors had *P*-values < 0.10. We excluded 11 cases from the bivariate analysis of age and the multivariate analysis because age at rash onset was uncertain. All analyses were weighted to adjust for the probability of selection at both sampling stages and for the sampling design of the study.

The number of cases and deaths in all measles outbreaks in Nepal during the study period was calculated by multiplying the number of study cases and deaths by the inverse of the probabilities of selection for each district and outbreak from both sampling stages. Because the study period covered only 7 months of 2004, the total number of cases and deaths occurring in outbreaks during the year was then increased by 19% (i.e. the proportion of outbreaks reported by the routine surveillance system before and after the study period in 2004) to obtain an estimate of the total number of cases and deaths in 2004.

Results

Study outbreaks

We initially selected 37 districts – 5 in the Himalayan mountains, 13 in the Himalayan foothills and 19 in the Ganges plains. Rubella was confirmed in 2 Ganges plains districts that were then excluded from the study, leaving a total of 35 districts. During the study period, 127 outbreaks were identified (1–11 per district, median 3) (Table 1). Of the 35 study outbreaks selected, 23 had been laboratory-confirmed as measles-only through the routine surveillance system. None of the 12 non-confirmed study outbreaks was located near a laboratory-confirmed rubella outbreak.

The number of cases identified per outbreak through routine outbreak investigations (7–376, median 28, mean 46) are shown in Table 1, as are the numbers of measles cases and deaths found during intensive house-to-house investigations (14–349 cases, median 113; 0–10 deaths, median 1). On average, nearly 3 times as many cases were identified through intensive investigations as through routine outbreak investigations.

Measles cases

In total, we identified 4657 measles cases (Table 2). Approximately 43% of them lived in highly or critically insecure areas. Most cases were children aged 5–14 years (56%) or 1–4 years (32%); few were < 1 year (6%) or ≥ 15 years (6%) of age. These age ranges make up 24%, 13%, 3% and 60% of the general population, respectively. Approximately half of the cases had received measles vaccine: 46% among those < 1 year of age; 64% among those 1–4 years; 49% among those 5–14 years, and 29% among those ≥ 15 years.

Mortality

Among the 4657 cases identified, 64 died within 30 days of rash onset and thus met the definition of a measles death. This yielded an overall nCFR of 1.1% (95% CI: 0.5–2.3) (Table 2). CFR ranged from 3.5% among cases < 1 year of age and 2.3% among cases 1–4 years of age, to < 0.5% among cases ≥ 5 years of age. Most deaths occurred within 1 (46%) or 2 (32%) weeks of rash onset (Fig. 1). Time to death varied significantly by age: death occurred within 1 week of rash onset in 86% of cases ≥ 5 years of age and in 63% of cases < 1 year of age.

In multivariate analysis, independent risk factors associated with a higher likelihood of death included living in critically insecure areas, living in the Himalayan mountains or the Ganges plains, being < 5 years old, being unvaccinated against measles, being the first measles case in the household, being self-medicated, not receiving vitamin A during the illness, being female and being part of a laboratory-confirmed measles outbreak.

Selected interactions

Increased risk of death among children < 1 year of age was most apparent in the Ganges plains, where the CFR was 6.1% (95% CI: 1.3–24.4). There appeared to be less access to health care in critically insecure areas than in moderately insecure ones, but the differences were not statistically significant: 35% versus 56% had received a dose of measles vaccine, 28% versus 48% had received vitamin A treatment during illness, and 32% versus 39% had been treated at a health-care facility, respectively. Approximately 90% of the cases and 88% of the deaths occurred in children between 9 months and 14 years of age; in this group, 47% of the cases and 92% of those who died had not received the measles vaccine.

Estimated national measles cases and deaths

After selection probabilities were applied, the estimated total number of cases in national outbreaks during the study period was 66 617 (95% CI: 42 671–90 562), and the estimated total number of deaths was 720 (95% CI: 234–1206). Overall, 137 (81%) of the 169 outbreaks reported through the routine surveillance system during 2004 occurred during the study period.

Table 1. **Data on selected measles outbreaks from 35 districts of Nepal, September 2004 to January 2005**

Region (no. of districts in region) and study district	Level of insecurity[a]	No. of outbreaks identified[b]	No. of cases identified	In selected outbreak					
				Lab-confirmed measles	No. of cases reported[b]	No. of subdistricts investigated	No. of cases identified	No. of deaths identified	Difference in no. of cases identified and reported
Eastern (15)									
Solukhumbu	Moderate	2	19	Yes	10	7	140	1	130
Panchthar 1	High	3	70	Yes	36	1	113	0	77
Panchthar 2	High	3	62	Yes	24	4	303	0	279
Jhapa	High	1	30	No	30	3	70	0	40
Saptari	Moderate	7	173	No	9	7	231	0	222
Central (19)									
Sindupalanchowk	Moderate	2	46	Yes	28	3	98	1	70
Nuwakot	Moderate	4	78	No	19	6	76	0	57
Dhading	Moderate	2	102	Yes	90	6	33	0	−57
Sindhuli	High	4	283	Yes	72	3	137	0	65
Chitawan	Moderate	1	23	Yes	23	1	18	0	−5
Bara	Moderate	2	87	No	40	1	57	0	17
Rautahat	Moderate	5	260	Yes	61	2	139	4	78
Sarlahi	Moderate	6	129	No	16	2	163	0	147
Mahottari	Moderate	11	289	Yes	18	3	254	3	236
Dhanusa	Moderate	1	30	Yes	30	1	43	0	13
Western (16)									
Mustang	Moderate	1	10	No	10	4	14	0	4
Baglung	Critical	6	62	No	39	3	135	1	96
Myagdi	Moderate	3	151	Yes	94	3	328	0	234
Parbat	Moderate	1	9	Yes	9	4	162	1	153
Nawalparashi	Moderate	4	90	Yes	35	2	148	2	113
Rupandehi	Moderate	4	67	Yes	7	4	133	2	126
Kapilvastu	Moderate	6	170	Yes	24	3	185	2	161
Mid-western (15)									
Salyan	Critical	1	23	Yes	23	2	144	1	121
Dailekh	Critical	1	83	No	83	1	77	2	−6
Jajarkot	Critical	1	376	No	376	1	109	10	−267
Banke	High	5	64	Yes	9	1	91	1	82
Dang 1	High	6	188	Yes	102	2	83	7	−19
Dang 2	High	7	131	Yes	15	2	94	6	79
Bardiya 1	High	4	295	Yes	60	2	251	8	191
Bardiya 2	High	6	201	Yes	29	2	349	0	320
Far-western (9)									
Bajhang	Critical	3	100	No	29	5	75	2	46
Bajura	Critical	2	35	Yes	14	1	152	5	138
Darchula	Critical	2	40	No	25	1	50	0	25
Kailali	High	6	249	Yes	102	1	101	2	−1
Kanchanpur	High	4	27	No	9	1	101	3	92
Total		**127**	**4052**		**1600**	**95**	**4657**	**64**	**3057**

[a] Based on United Nations official security phase designation from September 2002 through March 2004: "moderately insecure" were districts designated as either "phase I: warning" or "phase II: restricted" throughout the time period; "highly insecure" were districts sometimes designated as "phase III: relocation"; "critically insecure" were districts always designated as "phase III: relocation".

[b] Measles outbreaks and cases reported by district medical staff.

Table 2. **Risk factors for mortality among 4657 measles patients in selected districts of Nepal, September 2004 to January 2005**[a]

Variable	Cases		Deaths		Case–fatality ratio			Multivariate analysis[b]		
	n	Weighted %[c]	*n*	Weighted %[c]	Weighted %[d]	95% CI	Factor-level *P*-value	aOR	95% CI	Factor-level *P*-value
Total	**4657**		**64**		**1.1**	**0.5–2.3**				
Insecurity level[d]							0.17			0.003
Moderate	2222	57.2	16	31.0	0.6	0.3–1.3		Referent		
High	1693	32.8	27	51.8	1.7	0.4–6.6		1.8	0.5–6.2	
Critical	742	10.0	21	17.1	1.9	0.9–3.7		15.8	3.4–73.4	
Ecological zone							0.28			0.01
Himalayan mountains	377	6.4	4	5.9	1.0	0.6–1.8		3.7	1.0–13.6	
Himalayan foothills	1769	50.8	20	19.3	0.4	0.1–1.3		Referent		
Ganges plains	2511	42.8	40	74.8	1.9	0.8–4.7		11.9	2.6–55.3	
Age[e]							0.02			< 0.001
< 1 years	301	6.3	8	20.6	3.5	0.8–14.2		21.2	1.9–233.7	
1–4 years	1640	31.6	44	66.4	2.3	1.2–4.2		11.0	1.2–98.8	
5–14 years	2461	56.4	11	11.2	0.2	0.1–0.6		1.0	0.1–11.5	
15+ years	244	5.7	1	1.9	0.4	0.1–2.8		Referent		
Vaccination status							0.02			< 0.001
Vaccinated	2387	51.8	14	25.1	0.5	0.2–1.2		Referent		
Not vaccinated	2270	48.2	50	74.9	1.7	0.7–3.9		4.4	2.3–8.6	
Cases in household and place in order of cases within household							0.05			< 0.001
1 case	1190	24.3	23	41.9	1.9	0.7–4.7		3.3	2.1–5.0	
> 1 case in household, 1st case	1289	28.0	17	25.4	1.0	0.5–2.0		2.1	1.1–3.8	
> 1 case in household, not 1st case	2178	47.7	24	32.7	0.7	0.3–1.7		Referent		
Self-medication							0.11			0.04
Yes	672	12.0	15	23.4	2.1	1.0–4.3		2.7	1.1–7.0	
No	3985	88.0	49	76.7	0.9	0.4–2.3		Referent		
Vitamin A given during illness							0.03			< 0.001
Yes	2093	42.5	13	19.8	0.5	0.2–1.1		Referent		
No	2654	57.5	51	80.2	1.5	0.7–3.3		4.0	2.4–6.6	
Gender							0.09			0.04
Male	2284	49.5	25	39.4	0.9	0.4–2.0		Referent		
Female	2378	50.5	39	60.6	1.3	0.6–2.8		1.7	1.0–2.7	
Outbreak laboratory-confirmed							0.65			0.03
Yes	3499	84.9	46	88.9	1.1	0.5–2.7		3.4	1.2–9.8	
No	1158	15.2	18	11.1	0.8	0.3–2.2		Referent		
Development region							0.04			
Eastern	857	25.3	1	1.8	0.1	0.0–0.8				
Central	1018	13.8	8	12.4	1.0	0.6–1.6				
Western	1105	38.2	8	18.7	0.5	0.2–1.6				
Mid-western	1198	16.4	35	57.1	3.4	1.0–11.6				
Far-western	479	6.3	12	15.0	2.6	1.8–3.6				
Prevalence (%) of stunting (< 3SD) of preschool children in eco-developmental region[30]							0.05			
< 25	1664	51.4	6	12.0	0.3	0.1–0.8				
≥ 25	2993	48.7	58	88.1	2.0	0.9–4.3				

(Table 2, cont.)

Variable	Cases		Deaths		Case–fatality ratio			Multivariate analysis[b]		
	n	Weighted %[c]	*n*	Weighted %[c]	Weighted %[d]	95% CI	Factor-level *P*-value	aOR	95% CI	Factor-level *P*-value
Ethnic group							0.36			
Brahmin/Chhetri/ Thakuri	2392	53.5	45	74.0	1.5	0.6–3.6				
Newar/Tamang/ Sherpa/Magar/Rai/ Limbu/Chaudhary	1055	20.2	6	6.9	0.4	0.1–1.1				
Muslim	396	6.6	5	4.1	1.0	0.2–4.1				
Dalit	814	19.8	8	13.0	0.7	0.3–1.7				
Household size							0.52			
< 7 persons	2036	44.5	34	49.5	1.2	0.6–2.4				
≥ 7 persons	2621	55.5	30	50.5	1.0	0.4–2.5				
Treatment at health-care facility							0.31			
Yes	1583	36.6	20	24.8	0.7	0.3–1.6				
No	3074	63.4	44	75.2	1.3	0.5–3.0				
Treatment with traditional medicine							0.32			
Yes	1263	35.1	19	21.1	0.7	0.2–1.8				
No	3394	64.9	45	78.9	1.3	0.6–3.1				
Treatment by spiritual healers							0.11			
Yes	334	6.6	12	14.9	2.4	1.2–6.4				
No	4323	93.4	52	85.1	1.0	0.4–2.2				

aOR, adjusted odds ratio; CI, confidence interval; *n*, unweighted sample size; SD, standard deviation.

[a] All results are weighted except for sample sizes.

[b] Reduced model based on standard backward elimination.

[c] All percents were weighted to adjust for the probability of selection at both sampling stages and for the sampling design.

[d] Level of insecurity based on United Nations official security phase designation from September 2002 to end of March 2004: "moderately insecure" were districts designated as either "phase I: warning" or "phase II: restricted" throughout the time period; "highly insecure" were districts sometimes designated as "phase III: relocation"; "critically insecure" were districts always designated as "phase III: relocation".

[e] Eleven cases were excluded from the analysis of age groups and multivariate analysis due to lack of information on age at rash onset.

Thus, we estimate that approximately 82 243 measles cases (95% CI: 52 681–111 805) and 889 measles deaths (95% CI: 289–1489) occurred nationally in 2004 during measles outbreaks, for an overall estimate of 294 cases and 3.2 deaths per 100 000 people.

Among children < 5 years of age, an estimated 25 182 cases (95% CI: 16 676–33 688) and 626 deaths (95% CI: 142–1110) occurred during the study period. This yields a total of approximately 31 089 cases (95% CI: 20 588–41 590) and 773 deaths (95% CI: 175–1371) nationally in 2004 during measles outbreaks, for an estimated 805 cases and 20 deaths per 100 000 children < 5 years of age.

Discussion

To our knowledge, this is the largest study of measles CFRs to date and the first to be based on a nationally representative sample of measles outbreaks. Our data suggest that measles was a major cause of infection and death in Nepal in 2004, especially among children < 5 years of age. We also found that with the routine surveillance system cases and deaths were underreported and that the CFR based on a subnational study depends highly on the location investigated.

In May 2003, the World Health Assembly endorsed a resolution urging Member States to reduce measles deaths by 50% relative to 1999 estimates by the year 2005.[31] The number of measles deaths estimated from mathematical models based on the natural history of the disease depends highly on assumed CFRs.[1,2] However, surveillance-based CFR estimates may be unreliable. In Nepal, 2605 cases and 74 deaths were reported to the routine surveillance system nationally in 2004 (compared with 82 243 cases and 889 deaths estimated in the current study). These surveillance results gave a CFR of 2.8%, more than twice the nCFR estimated from this study, a discrepancy probably due to greater underreporting of measles cases than of measles deaths in the routine surveillance system. In other settings, this relationship may be reversed.[12] In 2005, an expert panel recommended more field studies on current measles CFRs, particularly in settings with a high burden of measles and suboptimal measles surveillance.[32] Recent studies have shown widely variable results.[6,12] The current study found one of the lowest CFRs reported to date, possibly because of regional variability and the use of a national sample of outbreaks rather than selected outbreaks in high-risk areas.

Insurgency in Nepal for the past 20 years has led to critical levels of insecurity in some areas. Our data suggest that measles cases in these areas had a 16-fold higher risk of death than cases in relatively secure areas, even after adjustment for other factors. Nearly two decades have transpired since publication of a landmark article by Toole et al.[33] on the impact of measles in complex emergencies and the importance of measles vaccination in low-security settings. It has also been more than a decade since the Sphere Project established minimum standards for humanitarian response. Nonetheless, measles continues to cause higher mortality in populations affected by conflict than in more stable populations,[34] perhaps partly as a result of reduced access to medical care (both preventive and curative). In our study, these variables were suggestive, though did not reach statistical significance.

A short time span from disease onset to death and reduced mortality among cases treated with vitamin A point to the need for rapid medical care for measles patients and for aggressive field-based treatment early in the outbreak. As in our study and others' published studies, we found that the CFR was highly dependent on age. Reducing high mortality rates among infants is challenging because measles vaccination is less effective at this age, and in our study most deaths occurred within the first week of life. Currently, the principal solution for preventing these deaths is to ensure herd immunity through high population coverage with measles vaccine.

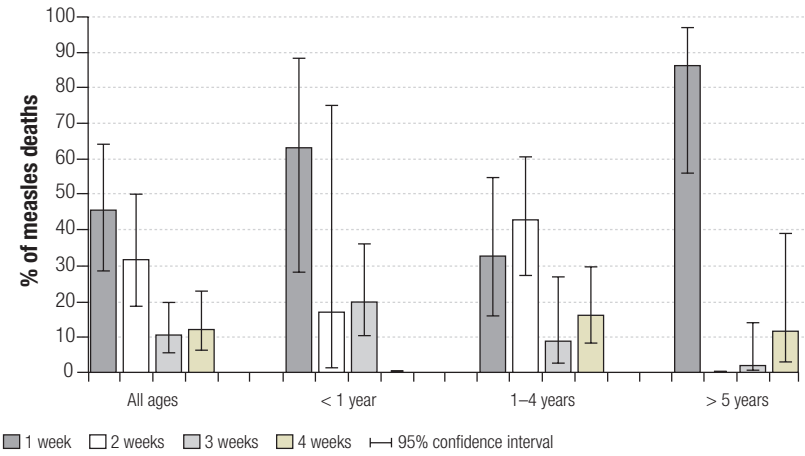
Limitations

This study has limitations. First, outbreaks, cases and deaths may have been misclassified. The clinical features of measles resemble those of rubella; thus, some outbreaks without laboratory confirmation may have been caused by rubella rather than measles. The observed CFR was slightly higher in laboratory-confirmed measles-only outbreaks (1.1%) than in outbreaks in which tests were not performed (0.8%). However, few rubella outbreaks were identified and none of the unconfirmed outbreaks were near a confirmed case. It is also possible that some cases were not measles since case status was based on respondent-reported symptoms and was not medically confirmed. However, the WHO case definition is thought to be appropriate for a confirmed measles outbreak without co-circulating rubella virus.[33] Some cases may have been missed, especially since the study was retrospective, although the potential for missing cases was minimized by house-to-house investigation and contact tracing, a recall period of < 11 months, and the use of a local calendar.

Second, the outbreaks in this study may not be representative of all measles outbreaks because information was incomplete and some areas were inaccessible. However, district medical officers reside within their assigned districts and learn of most outbreaks through established reporting channels, since there is much concern about measles among community members. Four of the selected outbreaks could not be accessed due to the insurgency (in one case, an interview team was held captive for 7 days by Maoist insurgents). Because these outbreaks and some sporadic cases were excluded, we may have underestimated morbidity and mortality rates, especially in areas difficult to access, as well as the differences between sites with different levels of insecurity.

Third, risk factors may have been misclassified. Ethnicity was assigned by researchers based on cases' family names and may have been misclassified in some instances. Vaccination status was primarily determined by questioning cases or caregivers because written documentation was seldom available. Non-differential misclassification, when misclassification of immunization status is the same across the groups being compared, would result in the OR moving towards the null and yield inappropriately low ORs. Finally, the study results may not apply to other years or other countries. Measles incidence and severity can vary temporally and geographically due to natural disease trends, routine vaccination coverage and large-scale vaccination campaigns.

Fig. 1. **Time from rash onset to death among measles cases, by age group, in selected districts of Nepal, September 2004 to January 2005**



Conclusion

This study suggests that measles continues to cause high morbidity and mortality in populations where security is poor and that high coverage with measles vaccine must therefore be maintained, especially in insecure areas.

Measles incidence was underreported when routine surveillance data were used. The geographical differences found in CFRs further suggest that subnational studies do not accurately represent the nCFR. A tendency to conduct in-depth investigation and CFR analysis of outbreaks with many reported deaths could lead to overestimated CFRs, and this could be exacerbated by publication bias in favour of studies yielding high CFRs. Therefore, additional CFR studies using nationally representative samples of outbreaks in other countries may be needed to expand our knowledge of the true global burden of measles and to improve measles control and elimination worldwide. However, such studies require substantial resources and extensive surveillance activities. ■

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Résumé

Décès dus à la rougeole au Népal : estimation du taux de létalité national

Objectif Estimer le taux de létalité (TL) pour la rougeole au Népal, déterminer le rôle de facteurs de risque tels que l'instabilité politique dans la mortalité par rougeole et comparer les résultats obtenus en utilisant un échantillon représentatif au plan national de flambées épidémiques et la surveillance de routine ou encore d'une étude localisée pour établir le taux de létalité national (TLn).

Méthodes Nous présentons ici une étude rétrospective des cas et des décès dus à la rougeole au Népal. Par un sondage aléatoire en deux étapes, nous avons sélectionné 37 districts, la probabilité de sélection étant proportionnelle au nombre de districts par région, puis nous avons sélectionné au hasard dans chaque district une flambée parmi celles survenues entre le 1er mars et le 1er septembre 2004. Nous avons identifié les cas en interrogeant un membre de chacun des ménages concernés et en retrouvant les contacts. Nous avons réalisé des analyses bivariées pour évaluer les facteurs de risque pour un taux de létalité élevé et déterminer le temps écoulé entre l'apparition de l'éruption et le décès. Nous avons déterminé la contribution de chaque facteur au taux de létalité par régression logistique multivariée. A partir des nombres de cas et de décès dus à la rougeole trouvés dans l'étude, nous avons calculé le nombre total de cas et de décès dus à cette maladie pour l'ensemble du Népal sur la période étudiée et en 2004.

Résultats Nous avons identifié 4657 cas de rougeole et 64 décès dus à cette maladie pendant la période et dans la zone étudiées. Nous avons ainsi abouti à un total d'environ 82 000 cas et 900 décès pour l'ensemble des flambées survenues en 2004 et à un TLn de 1,1 % (intervalle de confiance à 95 %, IC : 0,5-2,3). Ce taux variait de 0,1 % dans l'Est à 3,4 % dans la région moyen-orientale et atteignait ses niveaux les plus élevés dans les zones d'insécurité politique, dans les plaines du Ganges et parmi les cas âgés de moins de 5 ans. La prise de vitamine A et la vaccination antirougeoleuse jouaient un rôle protecteur. La plupart des décès sont survenus pendant la première semaine de maladie.

Conclusion A notre connaissance, il s'agit de la première étude du taux de létalité reposant sur un échantillon représentatif de flambées rougeoleuses. La surveillance de routine et les études portant sur une seule flambée peuvent ne pas fournir une valeur exacte du TLn. L'augmentation du nombre de morts liée à l'insécurité politique fait obstacle à la délivrance des services de santé. La brièveté du laps de temps entre l'apparition de la maladie et le décès, ainsi que la baisse de la mortalité résultant de l'administration de vitamine A, suggèrent la nécessité d'un traitement rapide sur le terrain, au tout début de la flambée.

Resumen

Mortalidad por sarampión en Nepal: estimación de la tasa de letalidad

Objetivo Estimar la tasa de letalidad por sarampión en Nepal, determinar el papel de los factores de riesgo -como la inestabilidad política- para la mortalidad por sarampión, y comparar el uso de una muestra de brotes representativa a nivel nacional y la vigilancia sistemática o los estudios localizados como medidas para calcular la tasa de letalidad nacional.

Métodos Se llevó a cabo un estudio retrospectivo de los casos de sarampión y las defunciones por esa causa en Nepal. Mediante muestreo aleatorio bietápico, seleccionamos 37 distritos con una probabilidad de selección proporcional al número de distritos en cada región y a continuación seleccionamos aleatoriamente dentro de cada distrito un determinado brote entre todos los que se habían producido entre el 1 de marzo y el 1 de septiembre de 2004. Se identificaron los casos entrevistando a un miembro de cada uno de los hogares y rastreando los contactos. Se realizaron análisis bifactoriales para evaluar los factores de riesgo de una tasa de letalidad alta y determinar el tiempo transcurrido entre la aparición de la erupción y la muerte. La contribución de cada factor a la tasa de letalidad se determinó mediante regresión logística multifactorial. A partir del número de casos de sarampión y de defunciones por esa causa hallados en el estudio calculamos el número total de casos y defunciones para todo Nepal durante el periodo estudiado y en 2004.

Resultados Identificamos 4657 casos de sarampión y 64 muertes atribuibles a la enfermedad en el periodo y zona estudiados. Eso se traduce en unos 82 000 casos y 900 defunciones en todos los brotes registrados en 2004 y una tasa de letalidad nacional del 1,1% (intervalo de confianza del 95%: 0,5–2,3). La tasa de letalidad se situaba entre el 0,1% de la región oriental y el 3,4% de la región medio-occidental, alcanzando su valor máximo en las zonas con inestabilidad política, en las planicies del Ganges y entre los menores de 5 años. El tratamiento con vitamina A y la inmunización antisarampionosa tenían un efecto protector. La mayoría de las defunciones se produjeron durante la primera semana de la enfermedad.

Conclusión Por lo que sabemos, éste es el primer estudio de la tasa de letalidad basado en una muestra nacionalmente representativa de los brotes de sarampión. La vigilancia

sistemática y los estudios de un solo brote no permiten calcular con precisión la tasa de letalidad nacional. El incremento de las defunciones asociado a la inestabilidad política constituye un reto para la dispensación de servicios de salud. El breve intervalo entre la aparición de la enfermedad y la defunción, así como la disminución de la mortalidad conseguida mediante el tratamiento con vitamina A, parecen indicar que es necesario tratar rápidamente a los afectados sobre el terreno al comienzo del brote.

ملخص

وفيات الحصبة في نيبال: تقدير معدل إماتة الحالات على الصعيد الوطني

الهدف: قدَّرنا معدل إماتة حالات الحصبة في نيبال، وتعرّفنا على دور عوامل الاختطار مثل القلاقل السياسية على وفيات الحصبة، وقارنّا استخدام عينة ممثلة للفاشيات على الصعيد الوطني في مقابل الترصُّد الروتيني أو دراسة محلية لتحديد المعدل الوطني للحالات المميتة.

الطريقة: هذه دراسة استعادية لحالات الحصبة ووفياتها في نيبال، فمن خلال اعتيان ثنائي المرحلة، قمنا باختيار 37 منطقة مع تحقيق التناسب بين احتمال الانتقاء وحجم العينة، ثم قمنا باختيار عشوائي لفاشية واحدة ضمن كل منطقة من بين جميع الفاشيات التي حدثت بين الأول من آذار/مارس والأول من أيلول/سبتمبر 2004. وتعرفنا على الحالات من خلال مقابلة أحد أعضاء كل أسرة من الأسر مع اقتفاء المخالطين. وأجرينا تحليلاً ثنائي التفاوت لتقييم عوامل الاختطار بالنسبة للمعدل المرتفع للحالات المميتة وللتعرف على الوقت الذي استغرقه المرض منذ بداية ظهور الطفح حتى الوفاة. وتعرّفنا على اسهام كل عامل في معدل إماتة الحالات من خلال التحوُّف اللوجستي المتعدد التفاوت. وقد انطلقنا من عدد حالات الحصبة وعدد الوفيات الذي وجدناه في الدراسة إلى حساب العدد الكلي لحالات الحصبة ووفياتها في جميع أنحاء نيبال أثناء فترة الدراسة وخلال عام 2004.

الموجودات: لقد وجدنا أن عدد حالات الحصبة 4657 وأن عدد الوفيات 64 خلال فترة الدراسة وفي المنطقة التي أجريت فيها؛ وهذا ما أدى إلى أن هناك 000 82 حالة و900 وفاة بسبب جميع الفاشيات في عام 2004، وبلغ معدل إماتة الحالات على الصعيد الوطني 1.1% (بفاصلة ثقة 95: 0.5-2.3) وقد تراوح معدل إماتة الحالات من 0.1% في المناطق الشرقية إلى 3.4% في المنطقة الغربية الوسطى، وكان أعلى ما يكون في المناطق التي تعاني من القلاقل السياسية، في سهول جانج وفي الحالات التي تقل أعمارها عن 5 سنوات. وقد كانت المعالجة بالفيتامين A والتمنيع ضد الحصبة أثراً اتقائياً، ووجدنا أن معظم الوفيات حدثت خلال الأسبوع الأول من المرض.

الاستنتاج: إن هذه هي الدراسة الأولى، على حسب ما نعلم، حول معدل إماتة الحالات التي بنيت على عينة ممثلة لفاشيات الحصبة على الصعيد الوطني. فالترصُّد الروتيني والدراسات التي أجريت على فاشية وحيدة قد لا تؤدي إلى نتائج دقيقة لمعدل إماتة الحالات على الصعيد الوطني. إن ازدياد معدلات الوفيات قد ترافقت مع القلاقل السياسية وهي تحد يواجه إيتاء خدمات الرعاية الصحية. إن قصر الفترة بين بدء المرض والوفاة ونقص معدل الوفيات الناجمة عن المعالجة بالفيتامين A يشير إلى الحاجة إلى معالجة سريعة ميدانية باكرة للفاشية.

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