# Risk factors for early infant mortality in Sarlahi district, Nepal

Joanne Katz,<sup>1</sup> Keith P. West Jr,<sup>1</sup> Subarna K. Khatry,<sup>2</sup> Parul Christian,<sup>1</sup> Steven C. LeClerq,<sup>1</sup> Elizabeth Kimbrough Pradhan,<sup>1</sup> & Sharada Ram Shrestha<sup>2</sup>

**Objectives** Early infant mortality has not declined as rapidly as child mortality in many countries. Identification of risk factors for early infant mortality may help inform the design of intervention strategies.

**Methods** Over the period 1994–97, 15 469 live-born, singleton infants in rural Nepal were followed to 24 weeks of age to identify risk factors for mortality within 0–7 days, 8–28 days, and 4–24 weeks after the birth.

**Findings** In multivariate models, maternal and paternal education reduced mortality between 4 and 24 weeks only: odds ratios (OR) 0.28 (95% confidence interval (CI) = 0.12-0.66) and 0.63 (95% CI = 0.44-0.88), respectively. Miscarriage in the previous pregnancy predicted mortality in the first week of life (OR = 1.98, 95% CI = 1.37-2.87), whereas prior child deaths increased the risk of post-neonatal death (OR = 1.85, 95% CI 1.24-2.75). A larger maternal mid–upper arm circumference reduced the risk of infant death during the first week of life (OR = 0.88, 95% CI = 0.81-0.95). Infants of women who did not receive any tetanus vaccinations during pregnancy or who had severe illness during the third trimester were more likely to die in the neonatal period. Maternal mortality was strongly associated with infant mortality (OR = 6.43, 95% CI = 2.35-17.56 at 0-7 days; OR = 11.73, 95% CI = 3.82-36.00 at 8-28 days; and OR = 51.68, 95% CI = 20.26-131.80 at 4-24 weeks).

**Conclusion** Risk factors for early infant mortality varied with the age of the infant. Factors amenable to intervention included efforts aimed at maternal morbidity and mortality and increased arm circumference during pregnancy.

**Keywords** Infant mortality; Infant, Newborn; Risk factors; Socioeconomic factors; Age factors; Maternal mortality; Health status; Tetanus toxoid/pharmacology; Smoking/adverse effects; Alcohol drinking/adverse effects; Randomized controlled trials; Nepal (*source: MeSH, NLM*).

**Mots clés** Mortalité nourrisson; Nouveau-né; Facteurs risque; Facteurs socio-économiques; Facteurs âge; Mortalité maternelle; Etat sanitaire; Anatoxine tétanique/pharmacologie; Tabagisme/effets indésirables; Consommation alcool//effets indésirables; Essai clinique randomisé; Népal (*source: MeSH, INSERM*).

**Palabras clave** Mortalidad infantil; Recién nacido; Factores de riesgo; Factores socioeconómicos; Factores de edad; Mortalidad materna; Estado de salud; Toxoide tetánico/farmacología; Tabaquismo/efectos adversos; Consumo de bebidas alcohólicas/efectos adversos; Ensayos controlados aleatorios; Nepal (*fuente DeCS, BIREME*).

**الكلمات المُتاحية**: وفيسات الرضع؛ الرضيع، حديث الولادة؛ عوامل الخطر؛ العوامل الاجتماعية الاقتصادية؛ عوامل العمر؛ وفيات الأمومة؛ الحالة الصحية؛ ذيفان التتانوس، فارماكولوجيسا ذيفان التتانوس؛ التدخين، التأثيرات الضائرة للتدخين؛ تعاطي الخمر، التأثيرات الضائرة لتعاطي الخمر؛ التجارب العشوائية المضبطة بالشواهد؛ نيبال. (المصدر: رؤوس الموضوعات الطية-المكتب الإقليمي لشرق المتوسط).

Bulletin of the World Health Organization 2003;81:717-725

Voir page 723 le résumé en français. En la página 723 figura un resumen en español.

يمكن الاطلاع على الملخص بالعربية في صفحة ٢٣٤

# Introduction

In spite of technical advances that have increased survival of children in developing countries, infant mortality rates are still at least 10 times higher in developing countries than in developed countries. Most infant deaths occur in the perinatal and neonatal periods, mostly due to prematurity, intrauterine growth retardation, and congenital causes; later deaths are more likely to be the result of infection (1). It may be useful to identify risk factors that predict early infant mortality, especially those that have the potential for intervention with modest resources.

Several studies have examined the role of risk factors for infant mortality (2-18). Others have identified risk factors for low birth weight, prematurity, and intrauterine growth retardation that are strongly associated with infant mortality

(19–25). Maternal characteristics, labour, and delivery are associated more strongly with perinatal and neonatal mortality; environmental factors are associated more strongly with later infant mortality (2, 4, 7–9, 11, 17, 18, 26).

We report the results of a large population-based study in rural Nepal, in which socioeconomic and demographic characteristics, reproductive history, substance abuse, physical work, morbidity and diet during pregnancy, characteristics of labour and delivery, and maternal mortality were analysed for mortality in babies aged less than six months.

# Materials and methods

A randomized community trial in Sarlahi district, Nepal, assessed the impact of a weekly nutritional supplement for all women of

<sup>2</sup> The Nepal National Society for Eye Health and Blindness Prevention, Kathmandu, Nepal. Ref. No. **02-000554** 

<sup>&</sup>lt;sup>1</sup> Division of Disease Prevention and Control, and the Center for Human Nutrition (CHN), Sight and Life Research Institute, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Room W5009, 615 N. Wolfe Street, Baltimore, MD 21205-2103, USA. Correspondence should be addressed to Dr Katz (email: jkatz@jhsph.edu).

childbearing age on maternal and infant health and survival (27, 28). A total of 270 communities in Sarlahi district, Nepal, were randomized to receive vitamin A (7000 µg retinal), betacarotene (42 mg or 7000 µg retinal equivalents), or placebo. Literate but minimally educated, female, village-based distributors provided a weekly supplement to all women of childbearing age and observed and recorded the receipt of the supplement each week, menses in the past week, whether the woman was pregnant, and the outcome of the pregnancy. Pregnancies identified from July 1994 that resulted in a live birth by March 1997 were included in the analysis.

Women who became pregnant provided an interview in the second and third trimesters and at three and six months postpartum. In the first interview, data on previous pregnancy history and child mortality, a one-week recall of illness and physical work activity, tobacco and alcohol consumption, and a sevenday food frequency questionnaire were obtained. The questions about morbidity, work activity, substance abuse, and diet were repeated in the third trimester, together with those about the socioeconomic status of the women. Illness in the three months leading up to delivery, tetanus vaccinations received during pregnancy, and the details of the labour and delivery were recorded at three months postpartum. Maternal and infant deaths were reported to the supplement distributor during their weekly visits and were confirmed by a supervisor. Deaths were grouped into those that occurred in the first seven days of life, at 8-28 days, and at 4-24 weeks. Only deaths of live-born, singleton infants were included, because multiple births had a much higher risk of mortality (29).

Risk factors were grouped into demographic and socioeconomic characteristics, prior pregnancy history, exposures and morbidity during pregnancy, and characteristics of labour and delivery (Box 1). Sex of the infant and postpartum death of the mother were grouped with demographic characteristics. Maternal mortality as a risk factor for infant mortality was calculated with only maternal deaths that preceded the death of the infant. Parity and gestational age of the infant at birth were included in all models of risk factors.

Gestational age was obtained from recall of the date of last menstrual period at the second trimester interview. If the woman could not recall this date, the gestational age was calculated from prospective weekly data about menses obtained by supplement distributors. For women with lactational or nutritional amenorrhoea, gestational ages were considered missing.

Risk factors that were significantly associated in bivariate analyses (P<0.05) with 0–7 day, 8–28 day, or 4–24 week mortality were included in all three logistic regression models in order to compare changes in risk factors as the infant aged. Maternal age and sex of the infant were included in all models, regardless of statistical significance. If risk factors measured in both the second and third trimesters were significant, the one that was more strongly associated with mortality was included in the model. The supplements did impact on maternal mortality and some aspects of maternal morbidity during pregnancy (27, 30). However, treatment was not included as a covariate, because supplementation had no impact on miscarriages, stillbirths, early infant mortality, or gestational age (28). The impact of maternal mortality and morbidity on infant mortality was thus not modified by supplementation.

The study was approved by the Joint Committee on Clinical Investigations of the Johns Hopkins School of Medicine and by the Nepal Health Research Council.

# Box 1. Risk factors investigated for associations with early infant mortality

#### Demographic and socioeconomic

- Maternal age
- Maternal and paternal education
- Occupation of the head of the household
- Caste
- · Household ownership of land, animals, and radios
- Number of household members
- House construction

#### **Prior pregnancy history**

- Parity
- Miscarriages and stillbirths
- Whether the most recent prior pregnancy ended in a live birth, miscarriage, or stillbirth
- · Number of prior live-born infants who had died

#### Exposures and morbidity during pregnancy

- Two prospective seven-day recalls and postpartum recall of severe illnesses in the third trimester
- Receipt of tetanus toxoid vaccine
- Work activity
- Alcohol and tobacco use
- Food frequency
- Characteristics of labour and delivery
- Place of delivery
- Type of person who delivered the infant
- Length of labour
- Whether anything was done to help deliver the infant (pressure, forceps, or caesarian section)
- Whether the placenta was delivered without assistance
- · How long after delivery the placenta was delivered

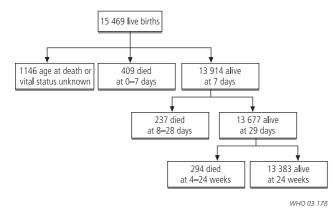
Community leaders provided community consent, but women gave individual verbal consent to participate.

## Results

A total of 15 469 singleton infants were born alive during the study (Fig. 1). The vital status at 24 weeks or age at death was available for 14 323 (92.6%) infants. A total of 409 infants died in the first week of life: 237 between eight and 28 days and 294 between four and 24 weeks of age. The mortality in the first week of life was 28.6 per 1000 live births, at 8–28 days was 17.0 per 1000 alive at eight days, and at 4–24 weeks was 21.5 per 1000 alive at four weeks. The cumulative mortality up to 24 weeks of age was 65.6 per 1000 live births.

Overall, 2771 (20%) women who gave birth were aged <20 years, and 3215 (22%) were primiparous. A total of 1788 (14%) mothers and 5671 (45%) fathers had received some formal education. Farming was the predominant occupation, with only 2443 (19%) household heads in business, private, or government service. Smoking during pregnancy was reported by 3739 (28%) women, and 1212 (9%) drank alcohol. Night blindness during the third trimester of pregnancy was reported by 1207 (8.6%) women. Only 401 (2.8%) women delivered in hospitals and 253 (1.8%) were delivered by a doctor; most women delivered at home with the help of family or untrained traditional birth attendants.

Risk factors in logistic regressions for at least one of the mortality time periods include maternal and paternal education; history of prior miscarriages, stillbirths, or prior deaths of liveFig. 1. Births and deaths of infants during a study in Sarlahi district, Nepal



born children; parity; gestational age; mid-upper arm circumference measured during the second trimester; the number of antenatal tetanus vaccinations; history of severe illness and vaginal bleeding in the last trimester; whether the woman delivered the baby on her own or was helped; the sex of the infant; and whether the mother died within 24 weeks of delivery (Table 1). The following demographic and socioeconomic factors were not associated with mortality: husband's occupation; household caste; ownership of land, animals, and household objects; house construction; and household size. Characteristics of the labour and delivery not associated with mortality were place of delivery; length of labour; whether the placenta was delivered with assistance; and time to delivery of the placenta. Infants delivered by the mother alone were at higher risk of death than those delivered by others, but it did not matter whether the person who helped the delivery was a relative, friend, traditional or trained birth attendant, or a doctor. The following exposures during pregnancy were not statistically significantly associated with mortality: swelling of the feet; convulsions; severe headaches; night blindness; accidents during the third trimester; cigarette smoking; chewing of tobacco or betel nut; alcohol consumption; heavy work (carrying of firewood, water, grain, fodder, or items to market; working in the fields; carrying rocks; or threshing grain); and consumption of meat, fish, eggs, or dairy products in the second or third trimesters. The unadjusted odds ratios for infant mortality if the mother reported night blindness during the third trimester were 2.46, 1.78, and 1.73 for 0-7 days, 8-28 days, and 4-24 weeks, respectively.

Parity and gestational age were risk factors associated with early infant mortality in all logistic regression models (Table 2). Their effects were slightly stronger for mortality in the first week of life, but the effect remained up to 24 weeks of age. Primiparous pregnancies were at higher risk than multiparous pregnancies, and the risk of death declined sharply with increasing gestational age until 42 weeks. A miscarriage in the previous pregnancy doubled the risk of death of a live-born infant in the first week of life, but it was not a risk factor for death after one week. The odds ratio for a history of at least one child death was double for deaths that occurred between four and 24 weeks of age. Boys were at higher risk than girls during the neonatal period but had a 27% lower risk of death subsequently.

Maternal and paternal education were important as predictors of mortality only for infants who died in the post-

neonatal period, with maternal education providing more protection than paternal education. Infants whose mothers had one or more tetanus vaccinations during pregnancy were at lower risk of death during the neonatal period than those who had not received any, in a dose–response manner. A history of severe illness in the third trimester was associated strongly with neonatal mortality, whereas vaginal bleeding was associated strongly with post-neonatal mortality. In total, 608 (50%) of the severe illnesses reported were fevers and 243 (20%) were diarrhoea or dysentery.

Maternal mortality was associated strongly with infant mortality at all ages, but the association increased as the infant aged. In the first week of life, 11 infants died whose mothers also died (not necessarily in the first week), and for two of these 11 infants, the infant died after the mother (18%), but six of 21 (29%) infants who died aged 1–24 weeks did so after their mother. Maternal death increased the odds of death for the infant by 6.43 in the first week of life, 11.73 from one to four weeks, and 51.68 from 4 to 24 weeks of life.

#### Discussion

Our findings were obtained in a large population-based study in an environment with minimal antenatal or trained obstetric care. Few studies of perinatal, neonatal, or infant mortality have been reported for such an environment (*3, 15, 17*). The infant mortality rate for Nepal was 75 per 1000 live births in 1999 (*31*). This rate is comparable with that in our study, if we assume that twothirds of infant deaths occur in the first six months of life and are likely to be representative of the mortality of the rural plains of Nepal, Bangladesh, and north India.

#### Associations with mortality

#### Gestational age

As expected, gestational age was associated most strongly with infant mortality in the first week of life, but it also had an association beyond this period. It could be argued that gestational age is in the causal pathway for mortality and should not have been included in the analysis. Regressions that did not include gestational age resulted in similar odds ratios for the risk factors remaining in the model, and no additional variables became statistically significant in its absence. This implies that gestational age played an independent role in early infant mortality that was unrelated to other factors that we were able to measure.

#### **Previous pregnancies**

Parity was associated with mortality during all periods up to 24 weeks of age, although the association was strongest for deaths in the first week of life. Numerous studies have shown that primiparous have higher mortality than multiparous pregnancies, but the risk is J-shaped, with the risk of death increasing with parity (2, 3, 5, 11, 14, 17, 32). This increase was not seen in our study for those with a parity of five or more.

Miscarriage of the previous pregnancy was a risk factor for mortality in the first week of life but not thereafter, whereas a history of mortality for live-born children was associated more strongly with infant mortality beyond the neonatal period. Early deaths are more likely to be associated with prematurity, and this would have a stronger association with previous miscarriage than previous child deaths (2, 5, 8, 11, 14).

#### Table 1. Mortality per 1000 live births by risk factors for early infant mortality and age at death

		Children's status					
Risk factor	Born alive	Died at 0–7 days	Alive at 8 days	Died at 8–28 days	Alive at 28 days	Died at 4–24 weeks	
Mean maternal age (years)	24.2 (5.4) <sup>a</sup>	23.9 (5.9)	24.3 (5.4)	23.6 (5.7)	24.23 (5.34)	24.8 (5.8)	
Arm circumference (cm)	21.3 (1.7)ª	21.0 (1.8)	21.3 (1.7)	21.3 (2.1)	21.3 (1.7)	21.3 (5.8)	
Maternal education							
None	11 187	30.0	10 851	17.9	10 657	23.4	
Any	1788	17.3	1757	12.5	1735	5.8	
Paternal education							
None	6971	32.3	6746	19.4	6615	26.2	
Any	5671	24.2	5534	14.3	5455	14.7	
Sex of infant							
Girl	7052	26.7	6864	15.6	6757	23.5	
Воу	7262	30.4	7041	18.3	6912	19.7	
Miscarriage in previous							
pregnancy No	10551	27.7	10 259	17.6	10 078	19.8	
Yes	1074	42.8	10 259	18.5	10 078	26.8	
Prior child deaths	1071	12.0	1020	10.5	1003	20.0	
None	8526	30.0	8270	16.8	8131	17.8	
Any	3118	26.3	3036	20.4	2974	27.9	
· · · ·							
Parity 0	3215	47.9	3061	25.5	2983	26.5	
1–2	5339	18.2	5242	14.9	5164	16.5	
3–4	3333	26.7	3244	10.2	3211	22.4	
≥5	2170	28.6	2108	20.4	2065	26.2	
Gestational age (months)							
28–31	842	102.1	755	38.4	726	38.6	
32–35	2172	46.5	2072	26.1	2018	32.2	
36–39	5818	18.2	5714	13.7	5636	20.0	
40–42 ≥43	3304 1379	17.6 20.3	3247 1348	10.8 18.5	3212 1323	14.3 19.7	
	1579	20.5	1540	10.5	1525	19.7	
Tetanus vaccinations during pregnancy							
None	3179	38.4	3057	21.9	2990	30.1	
1	5366	27.2	5220	16.1	5136	20.4	
>1	5431	21.4	5315	13.2	5245	15.6	
Severe illness in last three							
months of pregnancy	10 000		12 206	15 1	12 200	20.2	
No Yes	12 832 1207	26.7 38.9	12 396 1250	15.1 28.8	12 209 1214	20.2 24.7	
Vaginal bleeding in last three	1207	50.5	1230	20.0	1214	27.7	
months of pregnancy							
No	13 738	27.7	13 347	15.9	13135	20.0	
Yes	332	78.3	306	39.2	294	47.6	
Did anyone assist with the delivery?							
No	623	36.9	600	13.3	592	35.5	
Yes	13 443	27.3	13 076	16.5	12 860	20.0	
Maternal death							
No	14 093	27.7	13 570	15.5	13 360	19.7	
Yes <sup>b</sup>	47	234.0	39	179.5	32	437.5	

<sup>a</sup> Values in parentheses are standard deviations.

<sup>b</sup> In 118 maternal deaths, 32 infants died. The mother died before the infant (2/11 in the 0–7 day group, 5/7 in the 8–28 day group, and 1/14 in the 4–24 week group).

#### Table 2. Odds ratios from logistic regressions of risk factors for early infant mortality, by age at death

	Odds ratio for age at death					
Risk factor	0–7 days	8–28 days	4–24 weeks			
Maternal age (years)	1.02 (0.98–1.07) <sup>a</sup>	0.97 (0.92–1.02)	1.01 (0.97–1.06)			
Maternal education						
None	1.00	1.00	1.00			
Any	0.69 (0.43–1.09)	0.93 (0.52–1.64)	0.28 (0.12–0.66)			
Paternal education						
None	1.00	1.00	1.00			
Any	0.92 (0.69–1.22)	0.80 (0.56–1.16)	0.63 (0.44–0.88)			
Sex of infant						
Girl	1.00	1.00	1.00			
Воу	1.39 (1.07–1.80)	1.22 (0.88–1.69)	0.73 (0.54–0.99)			
Miscarriage in previous pregnancy	4.00	4.00	4.00			
No	1.00	1.00	1.00			
Yes	1.98 (1.37–2.87)	1.02 (0.57–1.82)	1.18 (0.73–1.91)			
Prior child deaths	1.00	1.00	4.00			
None	1.00 1.24 (0.85–1.80)	1.00	1.00 1.95 (1.24, 2.75)			
Any	1.24 (0.85–1.80)	1.40 (0.88–2.23)	1.85 (1.24–2.75)			
Parity	4.00	4.00	4.00			
0 1–2	1.00 0.29 (0.20–0.43)	1.00 0.60 (0.38–0.95)	1.00 0.40 (0.25–0.62)			
3–4	0.29 (0.20-0.43)	0.37 (0.18–0.75)	0.40 (0.22–0.72)			
≥5	0.21 (0.10-0.44)	0.79 (0.33–1.90)	0.37 (0.17–0.81)			
Gestational age		. ,				
28–31	1.00	1.00	1.00			
32–35	0.39 (0.27-0.58)	0.75 (0.43-1.31)	0.72 (0.42-1.25)			
36–39	0.18 (0.13-0.26)	0.39 (0.23-0.66)	0.47 (0.28-0.77)			
40-42	0.22 (0.14–0.33)	0.20 (0.10-0.39)	0.33 (0.19–0.60)			
≥43	0.19 (0.11–0.33)	0.59 (0.31–1.12)	0.38 (0.19–0.76)			
Mid–upper arm circumference (cm)	0.88 (0.81–0.95)	1.04 (0.94–1.14)	1.03 (0.94–1.13)			
Tetanus vaccinations during pregnancy						
None	1.00	1.00	1.00			
One More than one	0.72 (0.53–0.99) 0.57 (0.40–0.80)	0.65 (0.44–0.96) 0.51 (0.33–0.78)	0.87 (0.60–1.25) 0.69 (0.47–1.03)			
	0.37 (0.40-0.80)	0.31 (0.35-0.76)	0.09 (0.47-1.05)			
Severe illness in last three months of pregnancy						
No	1.00	1.00	1.00			
Yes	2.72 (1.99–3.74)	1.88 (1.20–2.94)	0.85 (0.50–1.44)			
Vaginal bleeding in last three months						
of pregnancy						
No	1.00	1.00	1.00			
Yes	1.75 (0.91–3.34)	2.04 (0.92–4.51)	3.37 (1.72–6.62)			
Did anyone assist in the delivery?						
No	1.00	1.00	1.00			
Yes	0.69 (0.37–1.27)	1.96 (0.61–6.24)	0.53 (0.29–0.95)			
Maternal death <sup>b</sup>						
No	1.00	1.00	1.00			
Yes	6.43 (2.35–17.56)	11.73 (3.82–36.00)	51.68 (20.26–131.80)			

<sup>a</sup> Values in parentheses are 95% confidence intervals.

<sup>b</sup> Adjusted for all the above variables except tetanus vaccinations, assistance with delivery, severe illness, and vaginal bleeding during the last three months of pregnancy which were not collected on women who died.

## Socioeconomic factors

Apart from maternal and paternal education, socioeconomic factors were not important predictors of mortality. This may be because more proximate factors were controlled for or because the variation in socioeconomic status in this community was relatively small compared with other studies. Our findings on education of the mother accord with those of many studies (3, 5, 15, 26, 33-35). Few studies have reported on paternal education (5). Although the model used only the presence or absence of schooling, a dose-response relationship with number of years of schooling was observed for paternal education. Too few women with more than a few years of schooling were included to examine such a relationship for maternal education. In this population, maternal and paternal education were independent predictors of mortality beyond the neonatal period, which suggests the importance of educated men in this paternalistic society, in addition to the role played by mothers in protecting the infant from mortality risks.

## Sex of the child

Our finding that boys were at higher risk of death in the early neonatal period accords with that of other studies (36, 37). The higher risk of death and its cultural determinants for girls beyond infancy have also been described on the Indian subcontinent (7, 38–40). The timing of the change from increased female-to-male survival, however, has not been reported as being as young as one month of age. The switch in survival advantage from girls to boys is more likely to have environmental (child-care and feeding practices) than biological explanations in this society, in which boys are favoured over girls.

#### **Tetanus vaccinations**

The protection from neonatal death afforded by tetanus vaccination may be due in part to the direct protection of the infant from neonatal tetanus. The greatest protection (adjusted odds ratios of 0.61 and 0.44 for one and two vaccinations relative to none, respectively) was conferred during the peak period for neonatal tetanus deaths (4-14 days). As part of the service provided by the research project to the community, pregnant women were encouraged to obtain tetanus vaccinations, and the project boosted supplies of vaccine in the district's health posts. It is also likely, however, that receipt of tetanus vaccinations was a surrogate for women who were more health conscious or proactive in seeking health care. A similar explanation is likely for women who delivered their baby themselves, without assistance from friends, relatives, or traditional birth attendants. Such women may have had a weaker social network for antenatal and postpartum care. This risk factor was only predictive of post-neonatal mortality, which further indicates that it probably represents care-seeking behaviour rather than something inherently risky about delivery without assistance.

#### Smoking and drinking

Although smoking during the second and third trimesters was associated with higher mortality in the first week of life, these associations were not statistically significant, either before or after adjustment for other factors. Although 28% of women reported smoking, the average number of cigarettes consumed per day was likely to be small (average of seven cigarettes per day in this population (41)). Only 9% of women reported drinking alcohol during pregnancy, but the amount consumed was not recorded, so it is difficult to draw conclusions about this exposure.

# Morbidity

Illness during pregnancy has been associated with numerous adverse outcomes of pregnancy (2, 17, 42-44). Although our recalls of symptoms of morbidity were relatively crude, they did indicate that serious illness during the last three months of pregnancy strongly predicted mortality during the neonatal period. Many of these illnesses were described as fevers, which may represent infections that could put the fetus at risk in the neonatal period. Another common morbidity was night blindness, usually in the third trimester (45, 46); the unadjusted odds ratios were not statistically significant when adjusted for gestational age, parity, and other maternal morbidities. Women who have night blindness are at increased risk of other morbidities during pregnancy, and this may explain the lower adjusted odds ratios (45).

### Anthropometric characteristics

Certain anthropometric characteristics of mothers are associated strongly with birth weight and infant mortality (2, 12, 14, 20, 23, 32, 47, 48). Weight gain during pregnancy was not recorded for these women, but mid–upper arm circumference in both the second and third trimesters was associated strongly with mortality of the infant in the first week of life. Mid–upper arm circumference is a measure of wasting in children, but it is not clear if these women were lacking fat or lean body mass and which of these might predict very early infant mortality. Mid– upper arm circumference may reflect pre-pregnancy weight, which is a strong predictor of birth weight and infant mortality (48, 49). This might also explain why the second trimester measurements were better predictors of early infant mortality than third trimester measurements.

## Maternal mortality

Maternal mortality was associated strongly with infant mortality. In the first week of life, infants were more likely to die before their mother, but thereafter, the mother was more likely to have died before the child. The prognosis for these children became increasingly bleak, because breastfeeding is universal and few other options for infant nutrition are available. Such infants were also likely to be weak or small because of birth complications that led to the death of the mother.

# Strengths and weaknesses of the study

This study has the advantage of being population based but has the inherent drawbacks of an observational study. Certain important confounders may not have been collected, and their absence may bias the resulting associations. For example, the lack of association between increased physical labour during pregnancy and adverse infant outcomes may have been the result of healthier women having greater work capacity than those who were ill during pregnancy. In addition, certain variables may not have been measured with enough precision to identify an association of importance. For example, the quantities of alcohol and tobacco consumed were not collected, so a dose– response analysis could not be performed.

# Possible interventions to reduce mortality

Factors potentially amenable to intervention would be reduction of maternal morbidity in the third trimester, or at least

identification of morbidities that would be important for referral. Improvement in mid–upper arm circumference of women before and during pregnancy would also be important, although it is recognized that these interventions need increased calories and protein intake (9). Maternal education is a longerterm intervention, but it is worthwhile in this environment, in which only 14% of women are literate. Finally, basic access to antenatal and obstetric services is likely to be important for reduction of maternal and infant mortality and should be emphasized as a priority in this environment.

# Conclusion

The large reduction in maternal mortality observed in this randomized trial has meant that pregnant women in the study area still receive antenatal vitamin A supplements from study personnel who are conducting other micronutrient trials in the same area (27). Antenatal vitamin A supplementation has not been adopted as a policy at the national level. Results of similar ongoing trials in Bangladesh and Ghana are awaited before the adoption of any global or national policies related to this intervention. Improvements in antenatal care in the study area have come largely from improved access to iron folate supplements, tetanus toxoid vaccine, deworming, and safe birthing kits provided by study staff through our ongoing research programmes, but access to skilled birth attendants and

emergency obstetric care has changed little. Maternal and newborn care is improving but remains quite inadequate, reflected by the fact that >90% of births still occur at home, attended primarily by family members, in most rural areas (50). The delivery of such services has not been helped by intense civil conflict in recent years. With a ceasefire under way, there is a push for improved national tetanus toxoid vaccine coverage, and with a Safe Motherhood programme being implemented in Nepal, it is hoped that access to and use of antenatal and obstetric care will improve in urban and rural areas.

**Funding:** This study was carried out by the Center for Human Nutrition and the Sight and Life Research Institute in the Department of International Health, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA, under Cooperative Agreement No. HRN-A-00-97-00015-00 between Johns Hopkins University and the Office of Health and Nutrition, US Agency for International Development, Washington, DC, and funding from the Bill and Melinda Gates Foundation, Seattle, WA, USA; Task Force Sight and Life, Roche, Basel, Switzerland; and United Nations Children's Fund, Nepal, in collaboration with the Nepal National Society for Eye Health and Blindness Prevention, Kathmandu, Nepal.

Conflicts of interest: none declared.

#### Résumé

#### Facteurs de risque de la mortalité infantile précoce dans le district de Sarlahi (Népal)

**Objectif** Dans de nombreux pays, la mortalité infantile (enfants de moins de 1 an) précoce n'a pas baissé aussi rapidement que la mortalité juvénile (enfants de moins de 5 ans). L'identification des facteurs de risque de la mortalité infantile précoce aiderait à concevoir les stratégies d'intervention nécessaires.

**Méthodes** Au cours de la période 1994-1997, 15 469 naissances vivantes d'enfants uniques dans les zones rurales au Népal ont fait l'objet d'un suivi pendant 24 semaines afin d'identifier les facteurs de risque de la mortalité entre 0 et 7 jours, 8 et 28 jours, et 4 et 24 semaines après la naissance.

**Résultats** Les modèles multivariés ont révélé que le niveau d'instruction de la mère et du père réduisait la mortalité entre 4 et 24 semaines seulement : odds ratio (OR) = 0,28 (intervalle de confiance (IC) à 95 % : 0,12-0,66) et OR = 0,63 (IC 95 % : 0,44-0,88), respectivement. Des antécédents d'avortement spontané lors de la grossesse précédente étaient un facteur prédictif de mortalité au cours de la première semaine de vie (OR = 1,98, IC 95 % : 1,37-2,87), tandis que le décès antérieur d'un enfant augmentait

le risque de décès postnéonatal (OR = 1,85, IC 95 % : 1,24-2,75). Une valeur élevée du périmètre brachial à mi-hauteur de la mère réduisait le risque de mortalité de l'enfant durant la première semaine de vie (OR = 0,88, IC 95 % : 0,81-0,95). Les enfants nés de femmes qui n'avaient pas été vaccinées contre le tétanos durant leur grossesse ou qui avaient souffert d'une maladie grave au cours du troisième trimestre risquaient davantage de mourir pendant la période néonatale. La mortalité maternelle était fortement associée à la mortalité infantile (OR = 6,43, IC 95 % : 2,35-17,56 entre 0 et 7 jours ; OR = 11,73, IC 5 % : 3,82-36,00 entre 8 et 28 jours, et OR = 51,68, IC 95 % : 20,26-131,80 entre 4 et 24 semaines).

**Conclusion** Les facteurs de risque de la mortalité infantile précoce variaient selon l'âge de l'enfant. Il faudrait pour les réduire concevoir des interventions visant à faire baisser la morbidité et la mortalité maternelles ou à augmenter le périmètre brachial durant la grossesse.

#### Resumen

#### Factores de riesgo de mortalidad infantil precoz en el distrito de Sarlahi (Nepal)

**Objetivo** Hay muchos países en que la mortalidad infantil (menores de un año) precoz no ha descendido tan rápidamente como la mortalidad en la niñez (menores de 5 años). La identificación de los factores de riesgo de la mortalidad infantil precoz ayudaría a diseñar las estrategias de intervención necesarias.

**Métodos** A lo largo del periodo 1994–1997, un total de 15 469 nacidos vivos de partos únicos en el Nepal rural fueron objeto de seguimiento hasta las 24 semanas de edad a fin de identificar los factores de riesgo de mortalidad correspondientes a los días 0–7, los días 8–28 y las semanas 4–24 tras el nacimiento.

**Resultados** Los modelos multifactoriales revelaron que la educación materna y paterna sólo reducía la mortalidad entre las 4 y las 24 semanas, con razones de posibilidades (OR) de 0,28 (intervalo de confianza del 95% (IC) = 0,12–0,66) y 0,63 (IC95% = 0,44–0,88), respectivamente. Los antecedentes de aborto espontáneo en el embarazo anterior permitían predecir la mortalidad en la primera semana de vida (OR = 1,98, IC95% = 1,37–2,87), mientras que una historia de defunción de un hijo anterior aumentaba el riesgo de muerte posneonatal (OR = 1,85, IC95% = 1,24–2,75). Un mayor valor del perímetro de la parte media del brazo materno reducía el

riesgo de mortalidad del lactante durante la primera semana de vida (OR = 0,88, IC95% = 0,81–0,95). Los lactantes de las mujeres que no recibieron vacuna antitetánica durante el embarazo o que sufrieron una enfermedad grave durante el tercer trimestre tenían más probabilidades de morir durante el periodo neonatal. La mortalidad materna estaba muy relacionada con la mortalidad infantil (OR = 6,43, IC95% = 2,35–17,56 en los días 0–7; OR = 11,73, IC95% = 3,82–36,00

en los días 8–28; y OR = 51,68, IC95% = 20,26–131,80 en las semanas 4–24).

**Conclusión** Los factores de riesgo de mortalidad infantil precoz dependían de la edad del lactante. Para reducirlos pueden concebirse intervenciones que tiendan a reducir la morbilidad y la mortalidad maternas o que aumenten el perímetro del brazo durante el embarazo.

### ملخص

# عوامل الخطر المسببة لمعدلات الوفيات الباكرة للرضع في منطقة سارلاهي في نيبال

في حين أدت سوابق وفيات الأطفال إلى زيادة مخاطر الوفاة بعد الولادة) إذ وصلت نسبة الأرجحية إلى ١,٨٥ عند فاصلة الثقة ٩٥٪، وتراوحت بين حلال الأسبوع الأول من العمر (نسبة الأرجحية = ٨٨, عند فاصلة للتقة٥٩٪، وتراوحت بين ٨١, -٥٩, ٥). أما الأطفال الذين وُلدوا لأمهات الثقة٥٩٪، وتراوحت بين ٢٨, -٥٩, ٥). أما الأطفال الذين وُلدوا لأمهات لم يتلقين تمنيعاً ضد التنانوس أثناء الحمل أو تعرضن لمرض وخيم في الأشهر الثلاثة الأخيرة من الحمل، فكانوا أقرب احتمالاً للوفاة في فترة الولادة .وارتبط معدل وفيات الأمومة ارتباطاً وثيقاً معدل وفيات الرضع (وصلت نسبة الأرجحية إلى الأولى بعد الولادة؛ ووصلت نسبة الأرجحية إلى ١٩,٧٦ عند فاصلة الأولى بعد الولادة؛ ووصلت نسبة الأرجحية إلى ١٩,٧٦ عند فاصلة المولى بعد السولادة؛ ووصلت نسبة الأرجحية إلى ١٩,٧٦ عند فاصلة المولى بعد الربولادة؛ ووصلت نسبة الأرجحية الماريما، منها السبعة المولى بعد الربولادة؛ ووصلت نسبة الأرجحية الى ١٩,٧٦ عند فاصلة المولى بعد الربولادة؛ ووصلت نسبة الأرجحية الى ١٩,٧٦ عند فاصلة المولى بعد الماريما، وتراوحت بين ٢٢,٨٠-٢،٠ عند فاصلة المولى بعد الماريما، وتراوحت بين ١٩,٠٠ مار ما يواليا السبعة الأولى بعد الماريما، ولادة إلى ١٩,٨٠ مار مار عدم المار ماريما، الماريمانة الماريمان الماريمان الماريمان الأولى بعد الماريمان التنان الماريمان ماريمان الماريمان الماريمان الماريمان الما

الوليد. وقد اشتملت العوامل القابلة للتدخل كلاً من الجهود التي تستهدف الحد من معدل الوفيات والمراضة لدى الأمهات، وزيادة محيط ذراع الأم أثناء الحمل.

# References

- Ashworth A, Waterlow JC. Infant mortality in developing countries. Archives of Disease in Childhood 1982;57:882-4.
- Mavalankar DV, Trivedi CR, Gray RH. Levels and risk factors for perinatal mortality in Ahmedabad, India. *Bulletin of the World Health Organization* 1991;69:435-42.
- Van den Broeck J, Eeckels R, Massa G. Maternal determinants of child survival in a rural African community. *International Journal of Epidemiology* 1996;25:998-1004.
- Binka FN, Maude GH, Gyapong M, Ross DA, Smith PG. Risk factors for child mortality in Northern Ghana: a case-control study. *International Journal of Epidemiology* 1995;24:127-35.
- Hull TH, Gubhaju B. Multivariate analysis of infant and child mortality in Java and Bali. *Journal of Biosocial Science* 1986;18:109-18.
- Vajpayee A, Govila AK. Effect of family structure, family size, and crowding on neonatal mortality in Indian villages. *Journal of Tropical Pediatrics* 1987;33:261-2.
- Hussain A, Ali SM, Kvåle G. Determinants of mortality among children in the urban slums of Dhaka city, Bangladesh. *Tropical Medicine and International Health* 1999;4:758-64.
- Alam N, van Ginneken JK. Repeated neonatal deaths in families with special reference to causes of death. *Paediatric and Perinatal Epidemiology* 1999;13:78-88.
- Ceesay SM, Prentice AM, Cole TJ, Foord F, Weaver LT, Poskitt EM, et al. Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. *BMJ* 1997;315:786-90.
- Comstock GW, Shah FK, Meyer MB, Abbey H. Low birth weight and neonatal mortality rate related to maternal smoking and socioeconomic status. *American Journal of Obstetrics and Gynecology* 1971;111:53-9.

الأهداف: لم تنخفض معدلات الوفيات الباكرة للرضع في العديد من البلدان بالسرعة التي انخفضت بها معدلات وفيات الأطفال. وقد يساعد التعرف على عـوامل الخطر ذات العلاقة بمعدلات الوفيات الباكرة على تصميم استراتيجيات للتدخل.

**الـطريـقة**: تم في الفترة من ١٩٩٤ إلى ١٩٩٧ مراقبة ١٥٤٦ طفلاً وُلدوا أحياءً بدون توأم في أرياف نيبال، وذلك حتى بلوغهم عمر ٢٤ أسبوعاً، بغرض استعراف عوامل الخطر ذات العلاقة بوفيات الرضع خلال الأسبوع الأول بعد الولادة، وفي الفترة من عمر ٨-٢٨ يوماً، وفي الفترة من عمر ٤ أسابيع إلى عمر ٢٤ أسبوعاً.

الموجودات في النماذج العديدة المتغيرات كان لمستوى تعلم الوالدين تأثير في خفض معدل وفيات الرضع في عمر ٤-٢٤ أسسبوعاً فقط وقد وصلت نسبة الأرجحية إلى ٢,٢٨ (عند فاصلة الثقة ٩٥٪، وتراوحت بين ٢,٦--٢,٠) لمستوى تعلم الأمهات، ووصلت إلى ٦,٣٠ (عند فاصلة الثقة ٩٥٪،وتراوحت بين ٤٤,٠-٨٨٨) لمستوى تعلم الآباء وأدى الإجهاض في حمل سابق إلى التبرؤ باحتمال وفاة الرضع في الأسسبوع الأول من حياقم (إذ وصلت نسبة الأرجحية إلى ١,٩٨ عند فاصلة الثقة ٩٥٪، وتراوحت بين ١,٣٢٧)،

- Leach A, McArdle TF, Banya WAS, Krubally O, Greenwood AM, Rands C, et al. Neonatal mortality in a rural area of the Gambia. *Annals of Tropical Paediatrics* 1999;19:33-43.
- Sachar RK, Soni RK. Perinatal mortality in rural Punjab a population-based study. *Journal of Tropical Pediatrics* 2000;46:43-5.
- 13. De Vaquera MV, Townsend JW, Arroyo JJ, Lechtig A. The relationship between arm circumference at birth and early mortality. *Journal of Tropical Pediatrics* 1983;29:167-74.
- 14. Barros FC, Victoria CG, Vaughan JP, Estanislau HJ. Perinatal mortality in southern Brazil: a population-based study of 7392 births. *Bulletin of the World Health Organization* 1987;65:95-104.
- 15. Chowdhury AKMA. Child mortality in Bangladesh: food versus health care. *Food and Nutrition Bulletin* 1988;10:3-8.
- Handayani T, Mujiani, Hull V, Rohde JE. Child mortality in a rural Javanese village: a prospective study. *International Journal of Epidemiology* 1983;12:88-92.
- Greenwood AM, Greenwood BM, Bradley AK, Williams K, Shenton FC, Tulloch S, et al. A prospective survey of the outcome of pregnancy in a rural area of the Gambia. *Bulletin of the World Health Organization* 1987;65:635-43.
- Edouard L. The epidemiology of perinatal mortality. World Health Statistics Quarterly 1985;38:289-301.
- 19. Berkowitz GS, Papiernik E. Epidemiology of preterm birth. *Epidemiological Reviews* 1993;15:414-43.
- 20. Malloy MH. Risk of previous very low birth weight and very preterm infants among women delivering a very low birth weight and very preterm infant. *Journal of Perinatology* 1999;19:97-102.
- 21. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. *New England Journal of Medicine* 1985;312:82-90.

- Weiner CP, Sabbagha RE, Vaisrub N, Depp R. A hypothetical model suggesting suboptimal intrauterine growth in infants delivered preterm. *Obstetrics and Gynecology* 1985;65:323-6.
- Siega-Riz AM, Adair LS, Hobel CJ. Maternal underweight status and inadequate rate of weight gain during the third trimester of pregnancy increases the risk of preterm delivery. *Journal of Nutrition* 1996; 126:146-53.
- 24. Victora CG, Smith PG, Vaughan JP, Nobre LC, Lombardi C, Teixeira AM, et al. Influence of birth weight on mortality from infectious diseases: a case-control study. *Pediatrics* 1988;81:807-11.
- 25. Read JS, Clemens JD, Klebanoff MA. Moderate low birth weight and infectious disease mortality during infancy and childhood. *American Journal of Epidemiology* 1994;140:721-33.
- Bernard RP, Sastrawinata S. Breast-feeding, birth-spacing and pregnancy care: prevalence and outcome. *Journal of Tropical Pediatrics* 1984;30:279-86.
- West KP Jr, Katz J, Khatry SK, LeClerq SC, Pradhan EK, Shrestha SR, et al. Double blind, cluster randomized trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. The NNIPS-2 Study Group. *BMJ* 1999;318:570-5.
- Katz J, West KP Jr, Khatry SK, Pradhan EK, LeClerq SC, Christian P, et al. Maternal low dose vitamin A or beta-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal. *American Journal of Clinical Nutrition* 2000; 71:1570-6.
- 29. Katz J, West KP Jr, Khatry SK, LeClerq SC, Christian P, Pradhan EK, et al. Twinning rates and survival of twins in rural Nepal. *International Journal of Epidemiology* 2001;30:802-7.
- 30. Christian P, West KP Jr, Khatry SK, Katz J, LeClerq SC, Kimbrough-Pradhan E, et al. Vitamin A or  $\beta$ -carotene supplementation reduces symptoms of illness in pregnant and lactating Nepali women. *Journal* of Nutrition 2000;130:2675-82.
- 31. United Nations Children's Fund. *State of the world's children*. New York (NY): UNICEF, 2000.
- Kusin JA, Kardjati S, de With C. Infant mortality in Madura, Indonesia. Implications for action. *Journal of Tropical Pediatrics* 1989;35:129-32.
- Esrey SA, Habicht JP. Maternal literacy modifies the effect of toilets and piped water on infant survival in Malaysia. *American Journal of Epidemiology* 1988;127:1079-87.
- 34. Cleland J, van Ginneken J. Maternal schooling and childhood mortality. *Journal of Biosocial Science* 1989;10:13-34.
- Cleland JG, van Ginneken JK. Maternal education and child survival in developing countries: the search for pathways of influence. *Social Science and Medicine* 1988;27:1357-68.
- Wells JCK. Natural selection and sex differences in morbidity and mortality in early life. *Journal of Theoretical Biology* 2000;202:65-76.

- Kline J, Stein Z, Susser M. Conception to birth. Epidemiology of prenatal development. New York (NY): Oxford University Press; 1989.
- Rousham EK. Socio-economic influences on gender inequalities in child health in rural Bangladesh. *European Journal of Clinical Nutrition* 1996;50:560-4.
- Chen LC, Huq E, D'Souza S. Sex bias in the allocation of food and health care in rural Bangladesh. *Population and Development Review* 1981;7:55-70.
- Das Gupta M. Selective discrimination against female children in rural Punjab, India. *Population and Development Review* 1987;13:77-100.
- Christian P, Khatry SK, Katz J, Pradhan EK, LeClerq SC, Shrestha SR, et al. Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal. A double-masked randomized community trial. *BMJ* 2003;326:571-6.
- Aaby P, Bukh J, Lisse IM, Seim E, de Silva MC. Increased perinatal mortality among children of mothers exposed to measles during pregnancy. *Lancet* 1988;1:516-9.
- Aaby P, Seim E, Knudsen K, Bukh J, Lisse IM, da Silva MC. Increased postperinatal child mortality among children exposed to measles during pregnancy. *American Journal of Epidemiology* 1990;132:531-9.
- Martius JA, Roos T, Gora B, Oeler MK, Schrod L, Papadopoulos T, et al. Risk factors associated with early-onset sepsis in premature infants. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 1999;85:151-8.
- 45. Christian P, West KP Jr, Khatry SK, Katz J, Shrestha SR, Pradhan EK, et al. Night blindness of pregnancy in rural Nepal nutritional and health risks. *International Journal of Epidemiology* 1998;27:231-7.
- 46. Christian P, West KP Jr, Khatry SK, LeClerq SC, Kimbrough-Pradhan E, Katz J, et al. Maternal night blindness increases risk of infant mortality in the first 6 months of life in Nepal. *Journal of Nutrition* 2001;131:1510-2.
- World Health Organization. Maternal anthropometry for prediction of pregnancy outcomes: memorandum from a USAID/WHO/PAHO MotherCare meeting. *Bulletin of the World Health Organization* 1991;69:523-32.
- Ahmed FU, Karim E, Bhuiyan SN. Mid-arm circumference at birth as predictor of low birth weight and neonatal mortality. *Journal of Biosocial Science* 2000;32:487-93.
- 49. Taggart NR, Holliday RM, Billewicz WZ, Hytten FE, Thomson AM. Changes in skinfolds during pregnancy. *British Journal of Nutrition* 1967;21:439-51.
- Osrin D, Tumbahangphe KM, Shrestha D, Mesko N, Shrestha BP, et al. Cross sectional, community based study of care of newborn infants in Nepal. *BMJ* 2002;325:1063-7.