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Manganese, Arsenic, and Infant Mortality in Bangladesh: An Ecological Analysis

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Manganese, Arsenic, and Infant Mortality in Bangladesh: An Ecological Analysis

Nicola Cherry, MD, PhD; Kashem Shaik, PhD; Corbett McDonald, MD; Zafrullah Chowdhury, MD

ABSTRACT. Recent studies in Bangladesh indicate that arsenic and manganese in tube-well water may increase the incidence of infant mortality. The study reported here examined whether these findings could be replicated. Data available from some 600 villages under the care of the nongovernmental organization (NGO) Gonoshasthaya Kendra included details of 29744 live births and 934 infant deaths in a 2-year period, with age and cause. These were analyzed by mean well levels of arsenic and manganese as reported by the British Geological Survey for the 12 upazillas. Odds ratios were calculated by age at death and cause. The effect of arsenic on all-cause infant mortality, although small and not significant, was consistent with earlier reports. The previous finding of an increased risk of infant mortality at concentrations of manganese $\geq$0.4 mg/L was not evident.

KEYWORDS: arsenic, epidemiology, heavy metals, infant mortality, water contamination

In Bangladesh, contamination of drinking water with arsenic is widespread and health effects from exposure in utero, childhood, and adult life have been widely studied in recent years (for example, references 1 to 5). Much less attention has been paid to other drinking water contaminants. The Government of Bangladesh, together with the British Geological Survey (BGS), analyzed water from 3534 tube-wells from 61 of the 64 districts in Bangladesh.[6] Of the 20 contaminants measured, arsenic and manganese were those that most commonly exceeded water quality standards: 42% of samples exceeded the World Health organization (WHO) guideline (10 μg/L) for arsenic and 35% exceeded the (then) WHO guideline of <0.5 mg/L for manganese. In general there was a low correlation between concentrations of manganese and arsenic, with only 8% of samples exceeding guidelines for both.

Manganese is a known neurotoxin and effects on health might be expected following cumulative exposures to high concentrations over many years or in infancy where absorption and retention may be higher than in older children.[7] It has also been suspected to be a reproductive toxin, with studies in man focussed on effects on male fertility of inhaled manganese in occupational settings (for example, reference 8). Vigeh et al[9] found higher manganese in cord blood (but lower in maternal blood) for growth-restricted newborns compared to those of appropriate weight for dates. A recent study by Hafeman et al[10] suggested that in Araihazar, Bangladesh, manganese in drinking water from the well used by the mother was associated with increased mortality in the first year of life. However, the study was limited, in that the data available did not include date, cause, or age at death. Ascertainment of deaths was based on a reproductive history taken at a first interview with 6707 women, of whom 1632 believed to have used a single well for most of their married lives, contributed to the analysis of 335 deaths before 1 year of age. The results presented were not consistent, with

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an adverse effect of manganese in drinking water in some subgroups studied but not in others, with the strongest effect in those using wells with high manganese but low arsenic concentrations. The authors concluded that their results were limited and preliminary, and in light of the methodological limitations and lack of a dose-response relationship, the association needed to be confirmed.

Uncertainties over level of risk at even moderate concentrations of arsenic and manganese are of serious concern to Gonoshasthaya Kendra (GK), a large nongovernmental organization (NGO) known internationally for its innovations in health care.[11] GK currently provides comprehensive services, mainly by well-trained paramedics, for an entire population of over a million inhabitants in some 600 villages across much of Bangladesh. As these villages are in areas that vary considerably in well water levels of arsenic and manganese, GK has successfully undertaken large-scale surveys, providing estimates of risk of arsenic related skin lesions[4,12] and stillbirth.[2] It was now important to assess whether or not similar exposures to arsenic and manganese increased the rate of infant mortality.

METHODS

The project was considered and approved by the University of Alberta Health Research Ethics Board.

Paramedics assigned to villages under the care of GK have routinely recorded detailed information on all pregnancies, including data on maternal reproductive history, education, and socioeconomic factors.[2] They also recorded details of all deaths of live born infants, including age (in days) and apparent cause. Information on all live births in GK villages in 2 years (Bangla 1409–1410, falling within 2001–2003 in the Western calendar) were available, together with the information on all deaths at less than 12 months in babies born in these 2 years. Birth and death data from the villages were reported by 15 Centres, grouped geographically into 12 upazillas (also called thanas), which form the lowest administrative area within Bangladesh. One upazilla had 3 Centres, one had two and the remaining 10 only one. Linkage between birth and death files at the individual level was not possible.

Our approach to exposure was essentially ecological and based on the National Hydrochemical Survey of Bangladesh undertaken by the British Geological Survey in 1998 and 1999.[6] This survey entailed an analysis of 20 constituents (mainly metals) in 3534 well water samples from tube-wells selected by systematic sampling in 61 of the 64 districts and 435 of 496 upazillas. This resulted in some 8 wells sampled per upazilla, on average 1 per 37 km^2. These results, published in detail, demonstrated that high levels of arsenic (>50 μg/L) were largely concentrated in the south and east of the country, whereas high levels of manganese (>0.5 mg/L) were on the west and north of the country, with relatively little geographic overlap.

Concentrations of arsenic and manganese were extracted from the BGS data set for the 12 upazillas, with 7 to 14 wells sampled in each. The mean concentration of each contaminant was taken to represent the exposure of the population living in that upazilla. Arsenic concentrations were considered by 3 levels, reflecting the WHO guideline of 10 μg/L and the Bangladesh limit of 50 μg/L. Manganese was grouped as in the Hafeman et al paper,[10] using the current WHO guideline of <0.4 mg/L. It was also grouped into 3 categories (<0.2, $0.2 \leq 0.8$, and ≥ 0.8) to allow examination of a dose-response.

Statistical methods

The numbers of births and deaths in each of the 2 years at each of 15 Centres were extracted, giving 30 estimates of mortality rates as data points for the analysis. The proportion of deaths was examined in relation to manganese (<0.4:≥ 0.4 mg/L) and arsenic (<10:$10 \leq 50$:≥ 50 μg/L) concentrations. Odds ratios were calculated, using a maximum likelihood estimator, clustered within upazillas, with each unit of observation being the number of deaths out of the number of live births in that upazilla. The blogit program within Stata[13] allows such a clustered analysis of grouped binomial data. Further analyses examined the relation of arsenic and manganese by age of death (≤ 7:8–28:≥ 29 days) and cause of death (low birth weight/prematurity, pneumonia, diarrhoea), and rates at higher levels of manganese (≥ 0.8 mg/L). We also examined the effect of possible covariates (first pregnancies, mothers with no formal education, and those designated as 'destitute,' 'very poor,' or 'poor' by GK for administrative purposes as of low socioeconomic status [SES]) as a proportion of mothers giving birth. For these further analyses we grouped the 30 observations into tertiles on each covariate and added them in turn to the blogit model as categorical variables.

RESULTS

There were 934 deaths within the first year of life amongst the 29744 live births recorded, an infant mortality rate of 31.4/1000. These included 404 deaths at <8 days, 205 at 8–28 days, and 325 at ≥ 29 days. Pneumonia was given as the most common cause of death at all ages (Table 1). Most deaths assigned to prematurity occurred within the first 7 days and most deaths from diarrhoea at greater than 1 month.

Concentrations of contaminants in the 114 individual wells sampled by the BGS in these 12 upazillas ranged from none detected (ND) to 166 μg/L for arsenic and from ND to 3.78 mg/L for manganese (Table 2, right columns). Means for the 12 upazilla ranged from 0.01 to 80.90 μg/L (arsenic) and 0.03 to 1.58 mg/L (manganese). In these samples (although not in Bangladesh as a whole), means for arsenic and manganese were positively correlated ($r = .49$, $p = .06$), with no upazilla having either low arsenic and high manganese or low manganese and moderate arsenic.

Table 1.—Cause of Death by Age at Death (Bangla Years 1409 and 1410)

	Age at death							
	≤7 days		8–28 days		29–364 days		Overall	
Cause of death	*N*	%	*N*	%	*N*	%	*N*	%
Pneumonia	172	42.6	116	56.6	170	52.3	458	49.0
Prematurity/low birth weight	164	40.6	50	24.4	48	14.8	262	28.1
Asphyxia at birth	23	5.7	11	5.4	23	7.1	57	6.1
Diarrhoea	2	0.5	6	2.9	42	12.9	50	5.4
Other[a]	43	10.6	22	10.7	42	12.9	107	11.5
Overall	404	100.0	205	100.0	325	100.0	934	100.0

[a]Including convulsions (24), jaundice (17), accident (9), and other (57).

Upazillas with manganese concentrations ≥0.4 mg/L had a higher mean proportion of women of low SES among those giving birth (86.0%) than those with manganese concentration <0.4 mg/L (70.3%) (Table 2, first 3 columns). Low SES was also related to deaths at ≥29 days: upazillas with more than 70% of births to low-SES women had a higher mean rate of such deaths (1.2%) than upazillas with fewer low-SES births (0.7%). SES was thus a confounder of the relation between manganese concentration and deaths at ≥29 days. The proportion of births to nulliparous women was related to neonatal deaths but not to arsenic or manganese in the wells. The proportion of women with no education was not related either to infant death or to arsenic or manganese concentrations.

Little relation was seen between mortality and either manganese or arsenic concentrations in the upazilla wells (Table 3 and Figures 1 and 2), although for both the marginal rate% increased with increasing concentration (manganese 3.01:3.33) arsenic (2.99:3.24:3.57). On univariate analysis, clustered by upazilla, neither manganese nor arsenic was significantly associated with mortality overall (Table 4). For manganese the risk of death in upazillas with concentrations ≥0.4 mg/L compared to those with concentrations <0.4 mg/L was highest (odds ratio [OR] = 1.49, 95% confidence interval [CI] 0.98–2.27) in deaths after the first month of life. Arsenic ≥50 μg/L was associated with deaths reported by the paramedic to be due to pneumonia (OR = 1.29, 95% CI 1.06–1.56). Adjustment for SES and year of birth affected these results only marginally: for deaths at ≥29 days, for example, the odds ratio for manganese ≥0.4 mg/L was reduced to 1.36 (95% CI 0.99–1.88) after adjustment for tertiles of low SES and year of birth of the infant. There was no evidence of a dose-response with manganese when the 3-level classification was used: the rates/100 were 3.44 (0≤0.2 mg/L); 2.82 (0.2≤0.8 mg/L); 3.36 (0.8≤1.6 mg/L).

Table 2.—Description of the Upazillas Included in the Study

						Arsenic			Manganese		
Upazilla	Births *N**	Deaths%*	Low SES%*	No education%*	Nulliparous%*	Mean	*SD*	Range	Mean	*SD*	Range
Bera	658.2	3.32	52.1	60.0	37.4	49.9	26.1	10.0–80.7	1.3	1.20	0.26–3.78
Char Fasson	593.3	2.17	61.6	62.1	38.0	4.54	1.72	2.7–7.4	0.03	0.01	0.02–0.05
Coxs Bazar Sadar	1009.0	3.75	85.8	74.7	33.2	0.26	0.38	0.05–1.0	0.38	0.28	0.00 –0.80
Gazipur Sadar	1095.5	3.87	90.4	66.8	26.8	0.31	0.71	0.05–2.4	0.22	0.22	0.10–0.78
Parbatipur	1341.5	1.90	89.4	69.9	25.5	0.23	0.51	0.05–1.5	0.28	0.17	0.06–0.58
Saturia	1143.5	2.62	94.7	91.2	26.2	16.19	19.3	0.05–62.8	1.58	1.03	0.46–3.16
Savar	642.0	3.24	77.9	61.4	32.5	0.16	0.32	0.05–1.0	0.07	0.14	0.01–0.43
Sherpur Sadar	1861.0	4.22	89.7	88.5	28.0	16.49	33.0	0.05–115.0	0.75	0.54	0.13–1.66
Shibganj (N)	482.5	4.16	83.1	63.5	35.9	19.2	27.1	0.05–63.9	0.71	0.28	0.41–1.28
Shibganj Sadar	1773.5	2.05	86.2	84.1	22.3	38.6	35.0	2.1–118.0	1.46	0.90	0.39–3.02
Sonagazi	1620.0	4.37	81.5	63.9	32.6	80.9	49.0	1.8–166.0	0.38	0.33	0.03–1.11
Sripur	742.5	2.61	74.7	69.7	34.8	1.1	2.99	0.05–8.5	0.13	2.33	0.01–0.70
Total	991.5	3.14	75.6	69.2	32.4	20.5	34.1	0.05–166.0	0.66	0.79	0.01–3.78

*Mean of birth reports for all villages for 2 years.

Table 3.—Infant Mortality (<12 Months) by Bangla Year of Birth and Concentrations of Arsenic and Manganese in Drinking Water

Manganese (mg/L)		Arsenic (μg/L) <10			10 ≤ 50			≥50			Overall		
		1409	1410	Both	1409	1410	Both	1409	1410	Both	1409	1410	Both
<0.4	Born	7824	8537	16361	[a]	[a]	[a]	572	712	1284	8396	9249	17645
	Died <12 months	265	224	489				17	25	42	282	249	531
	%	3.39	2.62	2.99				2.97	3.51	3.27	3.36	2.69	3.01
≥0.4	Born	[a]	[a]	[a]	4724	5357	10081	978	1040	2018	5702	6397	12099
	Died <12 months				175	152	327	33	43	76	208	195	403
	%				3.70	2.84	3.24	3.37	4.13	3.77	3.65	3.05	3.33
Overall													
	Born	7824	8537	16361	4724	5357	10081	1550	1752	3302	14098	15646	29744
	Died <12 months	265	224	489	175	152	327	50	68	118	490	444	934
	%	3.39	2.62	2.99	3.70	2.84	3.24	3.23	3.88	3.57	3.47	2.84	3.14

[a]No upazilla had concentrations in this range.

COMMENT

The results from this analysis for arsenic, although showing only a small effect (OR = 1.20 95% CI 0.91–1.59), closely replicate the results on arsenic and infant mortality in a large and meticulous study from Matlab, a high arsenic area of Bangladesh[1] where a relative risk of 1.18 (95% CI 0.99–1.41) was found for exposures of 10–163 μg/L, with higher (and significant) risk at concentrations not found in the present study. In contrast, they do not support the earlier report[10] of an increased risk of infant mortality in children born to mothers using drinking water from wells with higher manganese exposure: in that study an odds ratio of 1.8 (95% CI 1.2–2.8) was reported for those exposed to ≥0.4 mg/L of manganese. Hafeman et al[10] found no increasing risk with increasing concentrations of manganese beyond their second quintile of exposure: the risk was present in their data at concentrations of 0.5 to 1.0 mg/L and so should be seen, if indeed real, in the data considered here, particularly in the villages with mean concentrations of 0.8 to 1.6 mg/L. No such increase in risk was apparent.

Our study, as that of Hafeman et al,[10] has many (though different) strengths and limitations. The use of contemporary records of births and deaths with age and cause recorded by paramedics over a discrete period is a stronger design than the Hafeman et al analysis, which depended on maternal recall of events over, in some instances, 10 to 20 years. However, without linking the birth and death files at an individual level, we could not take full account of factors such as age, nutrition, and parity that might well influence infant

Table 4.—Age and Main Causes of Death by Mean Manganese and Arsenic Concentrations in Upazilla Wells

	Manganese (mg/L) <0.4		≥0.4			Arsenic (μg/L) <0.10		10 ≤ 50			≥50		
	n[a]	OR	*n*	OR	95% CI	*n*	OR	*n*	OR	95% CI	*n*	OR	95% CI
All deaths <12 months	531	1	403	1.11	0.76–1.61	489	1	327	1.09	0.70–1.68	118	1.20	0.91–1.59
Deaths													
<8 days	230	1	174	1.10	0.75–1.62	214	1	134	1.02	0.67–1.55	56	1.30	0.85–1.20
8–28 days	140	1	65	0.68	0.40–1.14	125	1	54	0.70	0.38–1.30	26	1.03	0.57–1.87
≥29 days	161	1	164	1.49	0.98–2.27	150	1	139	1.51	0.95–2.41	36	1.19	0.80–1.78
Cause of death													
'Prematurity'	161	1	101	0.91	0.59–1.41	151	1	78	0.84	0.51–1.37	33	1.08	0.72–1.64
Pneumonia	254	1	204	1.17	0.77–1.79	232	1	166	1.16	0.70–1.93	60	1.29	1.06–1.56
Diarrhoea	24	1	26	1.58	0.74–3.39	19	1	25	2.14	1.07–4.29	6	1.57	0.40–6.11
Number of births	17,645			12,099			16361		10,080			3302	
Number of upazillas	7			5			6		4			2	

[a]*n* = number of deaths.

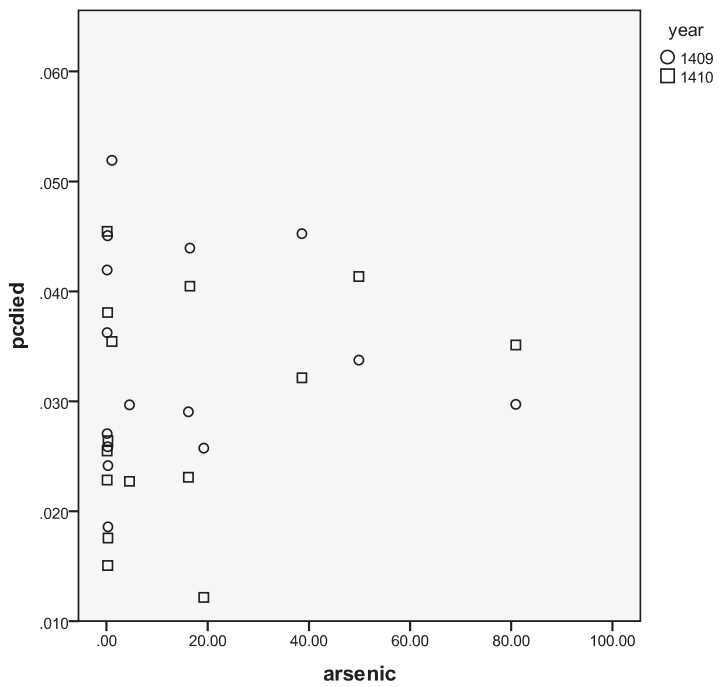

Fig. 1. Infant deaths per 100 live births by arsenic concentration.

mortality. Although there is no reason to suppose that such factors are strongly associated with drinking water contaminants, it is of interest that both in the present study and in that of Hafeman et al there was a positive relation between low SES and higher manganese concentration in well water. Hafeman et al, who found a highly significant relationship at the individual level, postulate residual confounding by SES as a possible explanation.

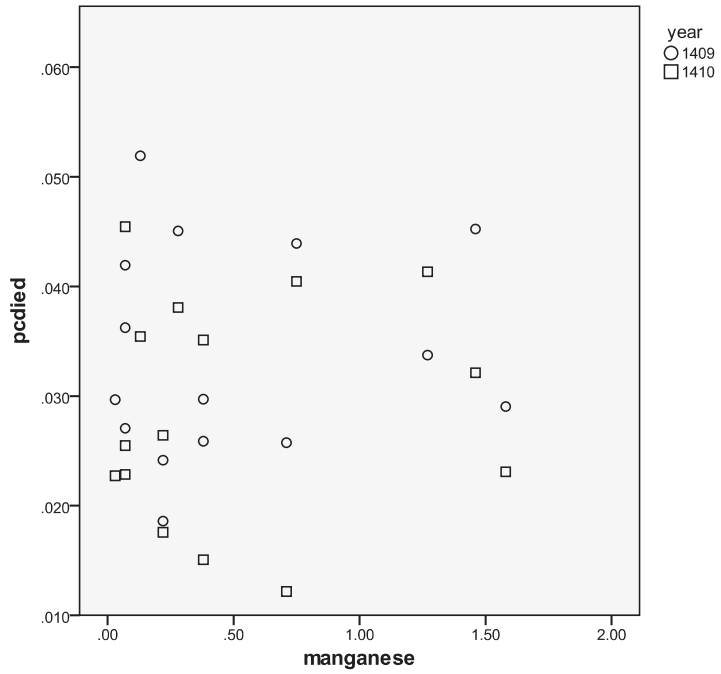

Fig. 2. Infant deaths per 100 live births by manganese concentration.

Second, the ecological assessment of exposure will certainly have resulted in misclassification of individual exposure. As evident from the range of values by upazilla shown in Table 2, there is considerable variation in level of contaminants between wells measured by the BGS in the same upazilla. A woman living in an area in which the well sampled had a mean manganese concentration of 0.4 might have been using water with a much greater or lesser concentration. Such variability reduces our ability to reject the hypothesis that manganese is related to infant mortality, as the effect of misclassification will be to bias the risk estimate towards the null. It is reassuring nevertheless that the BGS data used to classify the upazilla average exposure levels are the same as those used in our studies of skin lesions[4,12] and stillbirth[2] and indeed in a case-referent analysis of lung cancer,[5] all of which provided apparently rational results. The replication of Rahman et al's findings[1] for arsenic, which were based on individual well measurements, also gives credence to our ecological approach. Although only 7 to 14 wells per upazilla were sampled in the National Hydrochemical Survey, it is important to note that they were selected for each upazilla on a 3×3 grid, dividing the area into 9 approximately equal cells, in all of which at least one well was selected. Despite considerable variation in test results, the overall pattern after statistical smoothing was far from random.[6] The National Hydrographic Survey thus provides the country with unbiased but approximate estimates of exposure to arsenic, manganese, and other metallic contaminants. However, this cannot rule out all possibility of an ecological bias resulting from unspecified correlating factors. Although studies with individual measurements may also have unmeasured confounders, their role in ecological studies may be more complex[14] and constitute a further limitation.

It was argued by Hafeman et al[10] that any effect of manganese on infant mortality must come from water ingested by the infant rather than from in utero exposure or from breast milk. Although manganese is generally poorly absorbed from the gut, this may be less true in infants.[7] The weak suggestion in our study of increased risk in deaths after 28 days might be consistent with an increased exposure to manganese in drinking water with a greater use of supplementary feeding in older infants. Because no upazilla had high manganese and low arsenic, we were not able to test the somewhat counterintuitive observation from the Hafeman et al study that there was a risk from manganese only in the infants in whom arsenic concentration was <5 μg/L. We cannot either draw conclusions about the effects on infant mortality of higher concentrations of manganese (the BGS gives a maximum value, for Bangladesh as a whole, of 9.98 mg/L for manganese).

The replicability—or not—of the observation by Hafeman et al is an important public health question, in Bangladesh and elsewhere. Because concentrations of manganese and arsenic are shown by the BGS to be essentially uncorrelated across Bangladesh, any effort to mitigate the presumed effect of manganese would be different in different parts of the country and different wells than the urgently needed interventions to reduce exposures to arsenic in drinking water to concentrations of 50 μg/L or less. We concur with the observation of Hafeman et al[10] that the possibility of an association between manganese and infant mortality would best be tested in an a priori designed study with reliable methods for assessing exposure, outcome, and covariates. However, given the inconsistencies of their results and the failure of our ecological study to confirm their "preliminary finding of a possible association," the evidence taken together would seem too weak to justify redeployment of the very limited resources of a poor country already stretched to mitigate the looming disaster of arsenic contaminated drinking water.

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