Disease burden estimation to support policy decision-making and research prioritization for arsenic mitigation

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ABSTRACT

The main response to arsenic contamination of shallow tubewells in Bangladesh is the provision of alternative water supplies. To support decision-making in relation to alternative water supply selection, the Arsenic Policy Support Unit commissioned the development of a tool for estimating disease burdens for specific options using disability-adjusted life years as the metric. This paper describes the assumptions in dose-responses, relationships between microbial indicators and pathogens, water consumed and population characteristics used, and presents a case study of how the tool was applied. Water quality data and dose-response models were used to predict disease burdens due to microbial pathogens and arsenic. Disease burden estimates predicted by the tool were based on evidence in the published literature. There were uncertainties in key assumptions of water consumed and the ratio of microbial indicators and pathogens, which led to broad confidence intervals and the need to consider the results in a wider context and further research needs. Deep tubewells and rainwater harvesting had the lowest disease burden estimates, while pond sand filters and dug wells had much higher predicted disease burden due to frequent microbial contamination. The need for rigorous water supply protection through water safety plans was highlighted. At present, the risk assessment is useful for informing judgement by experienced water and health professionals and identifying key research questions. Improved arsenic dose-response models and a better understanding of the relationship between microbial indicators and pathogens in tropical settings are required.

Key words | arsenic, Bangladesh, DALYs, mitigation, risk assessment, water safety targets

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ABBREVIATIONS

APSU	Arsenic Policy Support Unit
As	arsenic
CFR	case fatality ratio
DALY	disability-adjusted life years
DTW	deep tubewell
DW	dug well
ESRD	end stage renal disease
HFT	human feeding trial
HUS	haemolytic uraemia syndrome
ICDDR,B	International Centre for Diarrhoeal Diseases Research, Bangladesh
ID50	the dose that leads to an infection in 50% of those exposed
μDPY	μDALYs per person·year
Pinf1	probability of infection when exposed to a dose of one pathogen
PSF	pond sand filter
QHRA	quantitative health risk assessment
RAAMO	Risk Assessment of Arsenic Mitigation Options
RW	rainwater harvesting system
STW	shallow tubewell
TTC	thermotolerant coliforms
UNICEF	United Nations Children's Fund
WHO	World Health Organization

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INTRODUCTION

Since the 1970 s, many millions of shallow tubewells have been sunk in Bangladesh and contributed to a reduction in diarrhoeal disease. Based on nationwide surveys and subsequent blanket screening, in the region of 20% of these shallow tubewells have arsenic concentrations in excess of the Bangladesh Standard of 50 $\mu g\,l^{-1}$ and a greater number in excess of the WHO provisional Guideline Value of 10 $\mu g\ l^{-1}$ (BGS and DPHE 2001; Ahmed 2003; NAMIC 2004). The Arsenic Policy Support Unit (APSU) is currently assisting the sector to make choices about which water supply options to use to reduce disease burdens that might be attributable to arsenic by adopting the conceptual framework proposed by Howard (2003) for the World Health Organization (WHO).

In water supply technology analysis the financial, technical, health, environmental and social feasibility of each option are considered. In relation to health, the technology presenting the lowest disease burden would always be preferred from the choice available given the constraints placed on that choice. Where the presence of the same hazard (contaminant) is being compared, the choice is simple: the water supply option with the lowest probable concentration of that hazard should be chosen. However, where different types of hazard are being compared the choice is more complex.

Howard *et al*. (2006) demonstrated that it was possible to gain value from using quantitative health risk assessment (QHRA) in a developing country to evaluate public health risks and investment decision-making. The QHRA process combines the best available expertise and evidence to make the best supportable risk estimates. Research needs are identified and, as new understanding emerges, predictions are revised. In the present study, a QHRA model that can support adaptive risk assessment and risk management was developed and applied in a water supply options analysis. The work was undertaken as part of the 'Risk Assessment of Arsenic Mitigation Options' (RAAMO) study funded by APSU. The generic quantitative risk assessment paradigm (Haas *et al*. 1999; WHO 1999; WHO/FAO 2003) was adopted in structuring the QHRA with the problem formulation being defined as 'Which arsenic mitigation option presents the lowest disease burden in a particular setting?'

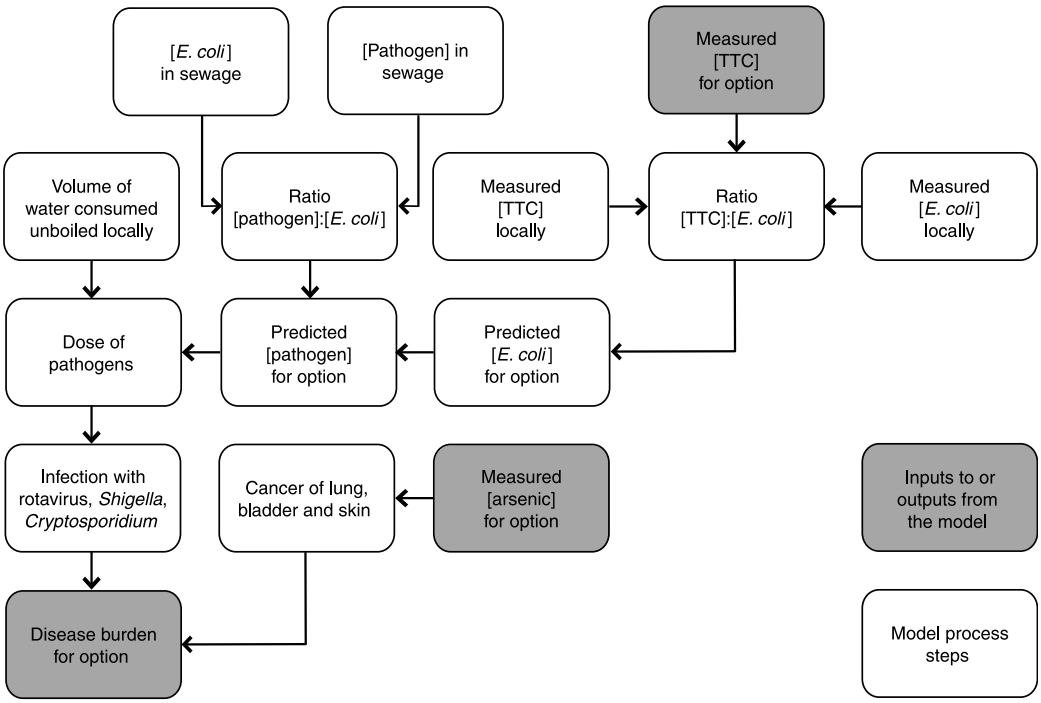

Figure 1 | Overview of model architecture showing inputs and outputs (shaded boxed) and process steps (unshaded boxes). TTC: thermotolerant coliforms.

Modelling approach

The WHO recommends the use of QHRA as part of the assessment of water supply options and to inform risk assessment and management (Deere *et al.* 2001; WHO 2004). The need for high-cost proprietary software and experience in mathematical modelling has historically limited the use of probabilistic QHRA to developed-world applications. However, Howard *et al.* (2006) demonstrated that a deterministic risk assessment model can be usefully applied in developing countries using available data as part of implementing a water safety plan.

In the present study a deterministic point value model, estimating median risks, was developed that could be run in any generally available spreadsheet package, making it generally applicable to developing world applications. The overall architecture of the model is illustrated in Figure 1. Two additional innovations were applied in building from the Howard *et al.* (2006) work.

First, to enable limited uncertainty analysis within the spreadsheet packages available and affordable to participating institutions in Bangladesh, the Slob (1994) uncertainty analysis methodology was used. This limited the frequency distributions that could be applied within the model to being either normal or lognormal (Slob 1994).

Second, both microbial and arsenic risks were combined in the same model enabling these risks to be balanced in assessing the health impacts of arsenic mitigation options. An important and challenging consequence of balancing risks in this way is that applying blatantly conservative assumptions will lead to biases that would prevent a fair assessment. Therefore, 'best supported' or 'most reasonable' assumptions must be used.

Hazard analysis

The hazards of interest were enteric pathogens and arsenic. WHO (2004) promotes the 'reference pathogen' concept in which the most resistant, abundant, infectious and virulent pathogens are used for risk assessment and in planning risk management. The basis for accepting the use of reference pathogens arises from the fact that not all of the approximately 150 waterborne pathogens can be modelled owing to lack of data. Furthermore, reference pathogens which can be one 'worst case' specific pathogen or a 'model' pathogen, which incorporates the characteristics of several key pathogens (infectivity, virulence, ubiquity, etc.), will represent most of the risk. In accepting this concept, model reference protozoan, bacterial and viral pathogens were defined, based on available data. The characteristics of these reference pathogens are shown in Table 1.

Model inputs

Ideally, the analysis of a suite of pathogenic, indicator and index organisms would be analysed in assessing microbial water quality as an input to health risk assessment. However, in reality risk assessments in developing countries are likely to use thermotolerant coliforms (TTC) as the principal microbiological input. *Escherichia coli* is rarely tested from community-managed supplies in developing countries because the field kits generally used do not test for *E. coli* and there are relatively few trained microbiologists and laboratories able to perform pathogen typing.

The TTC values used as the exemplary inputs were obtained from the use of membrane filtration field kits and laboratory analyses from statistically representative samples of technologies commonly used for arsenic mitigation (Ahmed *et al.* 2005). Some of these TTC counts were cross-checked for sanitary significance through a process of sampling a proportion of colonies from a proportion of plates for confirmatory testing for *E. coli*. The results indicated that *E. coli* was often present so that a significant proportion of TTC isolates were likely to be of faecal origin.

METHODS

Arsenic and TTC model inputs

Arsenic concentrations [As] and TTC concentrations [TTC] to be applied as inputs to the model were collected from a statistically representative set of four technologies commonly used for arsenic in both dry and monsoon seasons and from a smaller number of shallow tubewells (Ahmed *et al.* 2005). The measured [As] was applied directly as inputs to the dose-response relationship. The measured [TTC] was used as a basis for predicting pathogen concentrations [pathogen] since there was no other data

Table 1 | Summary of properties of the model reference pathogens

Model reference pathogen	Basis for concentration estimate	Basis for infectivity estimate	Basis for disease burden estimate
Virus	Total cultivable enteroviruses from sewage relative to *E. coli*	Human feeding trial of rotavirus	WHO generalised developing-world rotavirus
Bacterium	Total cultivable *Salmonella* spp. from sewage relative to *E. coli*	Human feeding trial of *Shigella dysenteriae*	WHO generalised *E. coli* O157:H7
Protozoan	Total confirmed *Cryptosporidium* oocysts from sewage relative to *E. coli*	Human feeding trial for *C. parvum*	WHO generalised *C. parvum*

from which to make such predictions, although this approach is recognised as being imperfect. Observed data were fitted to lognormal distributions using a simple maximum likelihood iteration spreadsheet as described by Haas (1994). Summary statistics for the water quality assessment results are given in Table 2.

Sanitary significance of thermotolerant coliforms

The proportion of TTC assumed to be of environmental origin (the remainder being assumed to be of faecal origin) is summarised in Table 3 and was defined as a lognormal distribution with a mean parameter of 15% and 5th and 95th percentiles of 7.5% and 30%, respectively. The TTC presumed to be of faecal origin were assumed to be *E. coli* for the purpose of predicting pathogen concentrations.

The reason that the percentage of TTC that are assumed to be of environmental origin is expressed, rather than the reverse (the percentage of TTC that are assumed to be of faecal origin) is because the former provides a more natural fit to the left-shifted skew of the lognormal distribution.

Ratio of [*E. coli*]:[pathogen]

Data from pathogen and *E. coli* monitoring in raw sewage provides an indication of the ratio of pathogens to *E. coli* that might be expected in human faecal matter deposited on land, in water and in latrines. Therefore, in predicting [pathogen] based on [*E. coli*] the ratio of [*E. coli*]:[pathogen] in reports of sewage quality monitoring were assessed as summarised in Table 4. Such an approach was previously used to support the assessment of risks to recreational water users (Craig *et al.* 2003). Datasets were selected that were large and in which there was a high degree of confidence because of involvement of at least one of the authors in their generation.

The pathogen concentration may be higher in Bangladesh than in the cited developed-world studies although this assumption is tentative and is based on the following observation. Stool specimens from 1 in 50 hospitalised patients in a hospital in Dhaka (regardless of presentation) were analysed to test for the presence of a limited number of important pathogens (ICDDR,B 2003). Results indicate that approximately 10% of samples are positive for rotavirus and

Table 2 | RAAMO water quality survey summary statistics

Technology	[As] $\mu g\,l^{-1}$		[TTC] cfu $100\,ml^{-1}$	
	Median	95%ile	Median	95%ile
Dry season				
Dug well	0.74	46	48	729
Pond sand filter	0.15	4.0	30	279
Deep tube well	0.41	8.6	0.04	4.6
Rain water system	< D.L.	< D.L.	2.0	135
Shallow tube well	151	382	0.05	78
Wet season				
Dug well	0.55	59	820	8,456
Pond sand filter	0.62	8.5	100	1,326
Deep tube well	0.78	5.7	1.2	65
Rain water system	< D.L.	< D.L.	0.75	244

DL = detection limit.

Table 3 | Exposure assessment assumptions

Model step	Median (90% confidence interval)	Basis
Proportion of TTC of environmental origin, the remainder assumed to be *E. coli*	15% (7.5 to 30%)	Ahmed *et al.* 2005
Ratio of [*E. coli*]:[virus]	10^5 (10^4 to 10^6)	Lodder and de Roda Husman 2005
Bacterium	10^5 (10^4 to 10^6)	M. Stevens, personal communication
Protozoan	10^6 (10^5 to 10^7)	D. Cunliffe, personal communication
Volume of unboiled water consumed per person per day	2.9 l day^{-1} (1.7 to 5 l day^{-1})	Bangladeshi community water intake survey from Watanabe *et al.* (2004)

a similar proportion are positive for *Shigella*. In contrast, pathogen prevalence in stools from an 18-month (1997 to 1999) prospective epidemiological study in Melbourne, Australia, found rotavirus in only 1.4% of faecal samples submitted from 791 study subjects reporting gastroenteritis (although only three were hospitalised, the study was following subjects at home) and did not isolate any *Shigella* (Hellard *et al.* 2001). The Hellard *et al.* (2001) study design was such that the results can be considered to be reasonably representative of a population in a developed-country city. Therefore, it's possible that the [*E. coli*]:[pathogen] ratio in Bangladesh is lower than that applied.

The 90% confidence intervals of the ratios were assumed to vary by approximately one order of magnitude and to decrease by approximately one order of magnitude from the mean value. The variation was introduced into the model to take account of two primary sources of variation and uncertainty.

Human faecal matter might be deposited on land and in latrines from where it might contaminate water sources by leaching or by surface water overflow. Surface flow, and even more so subsurface flow, could lead to a rise in the [*E. coli*]:[protozoan] ratio, which could conceivably increase by an order of magnitude at the same time as leading to a drop in the [*E. coli*]:[virus] ratio, which could conceivably decrease by around one order of magnitude due to the differential motilities and inactivation rates of viruses, protozoa and bacteria (Ferguson *et al.* in press).

Animal faecal matter is likely to be present and available to contaminate water sources since most rural households in Bangladesh keep at least one stock animal (45% cow, bull or ox, 26% goat or sheep and 77% poultry from the survey of Caldwell *et al.* 2003). The mammals will carry human-infectious strains of protozoan pathogens and both birds and mammals will carry human-infectious strains of bacterial pathogens (WHO 2004). However, neither are established sources of waterborne human-infectious enteric viruses (WHO 2004). Rodents may also contribute zoonotic pathogens, particularly for rainwater harvesting supplies. The mass of faecal matter produced by domestic animals is large, with, for example, 27.25 kg and 1 kg manure per day per cow and sheep, respectively, being reported (Olley & Deere 2003). Even assuming six persons per household (Caldwell *et al.* 2003) each producing a few hundred grams of faeces per day, domestic animals are likely to produce around one order of magnitude more faecal material than the amount produced by the human population and only the latter will use latrines. Furthermore, domestic animals, particularly juveniles, are known to have very high prevalence rates of protozoan pathogens, often reaching 100%, even in developed countries (Olley & Deere 2003; Cox *et al.* 2005). The effect of the presence of so much animal manure would be to drop the [*E. coli*]:[protozoan] ratio, conceivably by an order of magnitude, and raise the [*E. coli*]:[virus] ratio, conceivably by an order of magnitude.

The [*E. coli*]:[pathogen] ratios for the virus, bacterial and protozoan model reference pathogens are summarised in Table 3 and were assumed to be lognormal distributions with statistics, respectively, of mean 10^5, 10^5 and 10^6,

Table 4 | Data used to estimate [*E. coli*]:[pathogen] ratios in sewage

	Ratio [*E. coli*]:[Pathogen]		
Study	**Virus (enterovirus)**	**Bacteria (*Salmonella* spp.)**	**Protozoa (*Cryptosporidium*)**
USA, raw sewage (Rose *et al.* 1996)[1]	2.2×10^7	NR	1.5×10^7
Netherlands, raw sewage (Lodder & de Roda Husman 2005)[2]	1.4×10^6	NR	NR
Scotland, raw sewage (Robertson *et al.* 1999)[2]	NR	NR	6.3×10^6
England, raw sewage (Robertson *et al.* 1999)[2]	NR	NR	1.9×10^6
Scotland, raw sewage (Robertson *et al.* 2000)[2]	NR	NR	4.0×10^6
New Zealand raw sewage (Simpson *et al.* 2003)[2]	2.6×10^5	NR	NR
Brazil, raw sewage (Lopez-Pila & Szewzyk 2000 citing Mehnert and Stewien 1993)[3]	1.8×10^5	NR	NR
Australia, raw sewage (unpublished, D. Cunliffe, personal communication)[2]	NR	NR	$* 1.4 \times 10^6$
Australia, raw sewage (unpublished, M. Stevens, personal communication)[4]	5.9×10^4	3.8×10^5	5.7×10^6
Australia, raw sewage (unpublished, M. Stevens, personal communication)[4]	$* 1.1 \times 10^5$	$* 1.5 \times 10^5$	6.2×10^6
Average	4.8×10^6	2.6×10^5	5.7×10^6
Lognormal mean parameter (and lognormal 5th percentile and 95th percentile) values used in model[5]	10^5 (10^4, 10^6)	10^5 (10^4, 10^6)	10^6 (10^5, 10^7)

NR: Not reported.
*studies considered the most reliable based on the size of dataset, their currency and the level of experience of the laboratory employed.
[1]comparison with reported [TTC] no reported [*E. coli*].
[2][*E. coli*] not reported, compared with the average of the [*E. coli*] from the two Melbourne and the [TTC] from the US studies.
[3]comparison with rotavirus not enterovirus; pathogen recovery considered likely to be poor.
[4]Salmonella spp. most probable number (MPN) in secondary treated effluent compared with *E. coli* in that effluent. Results were positive in raw sewage making MPN indeterminate.
[5]based on the observed medians from the three studies indicated by '*' which were considered the most reliable based on the size of their datasets, currency and laboratory used.

5th percentile 10^4, 10^4 and 10^5, and 95th percentile 10^6, 10^6 and 10^7.

Volume of unboiled water consumed

Single-hit theory dose-response models applied for pathogens use the product of pathogen concentration and volume of water consumed to give the dose (Haas *et al.* 1999). Since the boiling process applied in cooking inactivates pathogens, the pathogen dose was calculated with reference to the volume of unboiled water consumed. Watanabe *et al.* (2004) analysed water consumption in two rural communities in Bangladesh. An average of 3.1 l day^{-1} (n = 38, range 1.3 to 6, average standard deviation of 1.0) of water was consumed during hotter periods of the year. Based on an analysis of variance the results did not differ significantly at the 95% confidence level between males or females or between the two communities assessed.

Based on these observations, the volume of water consumed is summarised in Table 3 and was assumed to

be a lognormal frequency distribution with a mean parameter of 2.9, an arithmetic mean and standard deviation of 3.1 and 1.0 l day^{-1}, respectively (as reported by Watanabe *et al.* 2004), and with 1.3 and 6 l day^{-1} as the 1st and 99th percentiles (the lowest and highest values reported by Watanabe *et al.* 2004), respectively. It was assumed that all water said to be 'directly' consumed in the Watanabe *et al.* (2004) study was unboiled as there were no indications to the contrary in the report; this was not explicitly stated.

Arsenic dose-response

A broad range of disease endpoints have been attributed to excessive arsenic consumption. The most recent broad review proposed that the strongest evidence related to cancers of the skin, lung and bladder and to cutaneous effects such as pigmentation changes and hyperkeratosis (Brown & Ross 2002) and these endpoints have been included in the present study, as summarised in Table 5. For the purpose of the present study, only these most strongly supported endpoints were considered in the model. It is acknowledged that a range of other endpoints have been attributed to excessive arsenic consumption based on less conclusive evidence, including cancers of the kidney, liver and prostate as well as cardiovascular, endocrine, reproductive and cognitive effects (NRC 1999, 2001; Abernathy, 2001; Wasserman *et al.* 2004).

To enable the interpretation of specific data for specific technology options, the present study required a model that

Table 5 | Basis for dose-response assessment assumptions

Model step	Value	Basis
Arsenic dose-response relationships	Skin cancer prevalence given arsenic concentration in water	Yu *et al.* (2003) (citing the analysis of Brown *et al.* 1989 based on south-western Taiwanese data of Tseng *et al.* 1968; Tseng 1977)
	Internal cancer incidence (lung and bladder) given arsenic concentration in water	Yu *et al.* (2003) (citing the analysis of NRC 1999, 2001 based on Taiwanese data of Chen *et al.* 1985 and Wu *et al.* 1989)
Arsenic disease risk as input to DALY calculation	Annual incidence (prevalence converted to annual incidence for arsenicosis and skin cancer)	Havelaar & Melse (2003)
Microbial pathogen dose-response relationships	Daily probability of infection for viruses given dose ingested	Gerba *et al.* (1996) (citing Ward *et al.* 1986 for rotavirus)
	Daily probability of infection for bacteria given dose ingested	Holcomb *et al.* (1999) (citing Levine *et al.* 1973 for *Shigella dysenteriae*)
	Daily probability of infection for protozoa given dose ingested	Messner *et al.* (2001) (citing DuPont *et al.* 1995, Okhuysen *et al.* 1999 and Chappell *et al.* 1999 for *Cryptosporidium parvum*)
Microbial infection risk as input to DALY calculation	Annual probability of infection given daily probability of infection	Teunis *et al.* (1997)
DALYs per infection (microbial) or per case (disease)	Virus 2.4×10^{-3} Bacterium 1.3×10^{-2} Protozoan 1.4×10^{-4} Skin cancer 1.18 Lung cancer 16.29 Bladder cancer 13.67	Primarily Havelaar & Melse (2003), modified to take into consideration local life expectancy, assumptions relating to levels of immunity and omitting less well-supported associations and sequelae

could provide disease burden estimates for any arsenic concentration within the dynamic range likely to be relevant to the Bangladesh arsenic mitigation programmes. Therefore, for this study, dose-response models that use a continuous range of arsenic input values and that are tailored to application in Bangladesh were sought. A number of recent studies have described dose-response models specifically adapted to US circumstances (NRC 1999, 2001), optimised to cope with very low doses (3 to 20 $\mu g l^{-1}$) and a response in the US population (larger bodyweight and lower water consumption than Bangladesh). Another recent study (Lokuge *et al.* 2004) that focused on Bangladesh at the national level applied categorical dose inputs (categories of, rather than continuous, arsenic concentrations). Yu *et al.* (2003) described dose-response models developed specifically for Bangladesh that provide a relationship between observed health effects in exposed populations and continuous values of measured arsenic concentrations in wells used as the community water sources.

The dose-response models presented by Yu *et al.* (2003) enable prediction of all the disease endpoints selected for this study. The skin lesion (arsenicosis) predictions were not included because there is currently no consensus about the severity weight to be allocated to arsenicosis. The skin cancer predictions are based on the analysis of Brown *et al.* (1989), which is in turn based on Taiwanese data of Tseng *et al.* (1968) and Tseng (1977). Internal cancer (lung and bladder) predictions are based on the analysis of NRC (1999, 2001), which are in turn based on the Taiwanese data of Chen *et al.* (1985) and Wu *et al.* (1989).

In applying models fitted to data from south-western Taiwan and West Bengal, it was assumed that the bodyweight, nutritional status and direct and indirect volumetric water intakes of the current Bangladesh population are reasonably similar to those of the historical populations to which the dose-response models were fitted. Note that such an assumption was not made by USEPA in translating observations from the Asian studies to the US since the bodyweights of the latter are significantly higher and water volumes consumed significantly lower and a correction factor was applied (NRC 2001). No basis to apply any such correction factors for the Bangladesh situation was found, however, and what comparative data was available suggested that the populations are reasonably comparable and that the Yu *et al.* (2003) models are the most appropriate yet published for the current study.

For example, Watanabe *et al.* (2004) reported an average total water consumption (direct and indirect through incorporation into food and both boiled and unboiled) of 4.6 and 4 l day^{-1} for males and females, respectively, in Bangladesh, which was very similar to values that Watanabe *et al.* (2004) derived from their review of studies from Taiwan (4.5 and 3 l day^{-1}, respectively) and West Bengal (5 and 4 l day^{-1}, respectively). In addition, as noted by Lokuge *et al.* (2004), the current Bangladeshi population is fairly similar, in terms of relevant factors, to the Taiwanese population from which much of the arsenic dose-response data are derived.

Since the selected dose-response models were fitted to the relationship between observed health effects and the measured concentrations of arsenic in community water sources, the arsenic concentration alone provided the model input for arsenic. Incidence rates provided the inputs to the DALY estimation so prevalence rates were converted to annual incidence rates by dividing prevalence by average symptom duration in years (summarised in Table 5).

Microbial dose-response

The dose-response relationships for the model reference pathogens were based on reported human-feeding-trial (HFT) data as summarised in Table 5 and are detailed as follows. For 'virus' the rotavirus model of Gerba *et al.* (1996) (citing the HFT of Ward *et al.* 1986) was applied with a P_{inf1} (probability of infection for dose of one) of 27% and an ID50 (the dose leading to a probability of infection of 50% of those exposed) of 6. This model was selected for the viral model reference pathogen since it was based on rotavirus, which is an endemic and routinely surveyed cause of infection in Bangladesh (ICDDR,B 2003). A beta-Poisson distribution was selected because it has been corroborated and widely used since being proposed by Gerba *et al.* (1996).

For 'bacterium' the *Shigella dysenteriae* model of Holcomb *et al.* (1999) (citing the HFT of Levine *et al.* 1973) was applied with a P_{inf1} of 1% and an ID_{50} of 219. This model was selected for the bacterial model reference

pathogen since it was based on *Shigella*, which is an endemic and routinely surveyed bacterial infection in Bangladesh (ICDDR,B 2003). The Weibull-gamma relationship was selected since it provided the smallest over-estimate at below-threshold doses from the acceptable-fitting inflexion models.

For 'protozoan' the 'unknown strain' model for *Cryptosporidium parvum* of Messner *et al.* (2001) (citing the HFTs of DuPont *et al.* 1995; Okhuysen *et al.* 1999 and Chappell *et al.* 1999) was applied leading to P_{inf1} of 2.8% and an ID_{50} of 25. This model was selected for the protozoan model reference pathogen since it was based on *Cryptosporidium*, which is generally a more environmentally mobile, persistent and infectious pathogen than the alternatives *Giardia* and *Entameoba*, and because it was based on a hierarchical Bayesian analysis of human dose response to several strains, capturing the information from three HFTs, which provided more confidence in the model than those described for the alternatives *Giardia* and *Entameoba* (Teunis & Havelaar 2002).

The daily dose of pathogens consumed was converted to a daily probability of infection according to these dose-response relationships to give an infection endpoint prediction for each pathogen. The daily probability of infection was converted to an annual incidence of infection as described by Teunis *et al.* (1997), which provided the input to the DALY calculation.

DALYS

In general, DALYs were determined as described for waterborne disease by WHO (2004) and Havelaar & Melse (2003) as summarised in Table 5. Where a number of alternatives were proposed, the developing world assumption was applied. In addition, a number of modifications were made where relevant national data was available.

Life expectancy in Bangladesh at birth in 1999 was stated as 60.8 for males and 59.6 for females (BBEIS 2004). Average life expectancies at birth of 62 were, therefore, applied for both sexes in this study. The use of national life expectancy was preferred because, as noted by Howard *et al.* (2006), this provides a more realistic comparison for national planning. The ratio of males to females was 103.8:1 based on the draft 2001 census summary (BBS 2004) and where appropriate this ratio was applied in deriving averaged community disease burdens. The age distribution applied based on the 1991 census was applied as described by Yu *et al.* (2003) since more recent figures from the 2001 census were not available at the time of the study.

The rotavirus, *Cryptosporidium* and *E. coli* O157:H7 DALY severity weight estimates described by Havelaar & Melse (2003) were selected for viral, protozoal and bacterial disease, respectively. Sequelae, such as haemolytic uraemia syndrome (HUS) and end-stage renal disease (ESRD) for bacteria and AIDS-related symptoms for protozoa were excluded because of a lack of reliable data. This omission was consistent with the omission of the less well-supported disease endpoints for arsenic.

Disease burden per case was determined for internal and skin cancer endpoints as described by Havelaar & Melse (2003). No global burden of disease (Murray & Lopez 1996) severity weights were described for arsenicosis skin lesions and this endpoint was omitted from the present study and a generic research need was identified.

As an additional modification, background levels of immunity to the viral, bacterial and protozoan reference pathogens were assumed to be relatively high owing to the high background levels of disease borne by hygiene-related and other routes of transmission. These assumptions were based on the opinion of local health sector professionals from WHO, UNICEF and ICDDR,B (International Centre for Diarrhoeal Diseases Research, Bangladesh) rather than objective data.

For the model viral reference pathogen, due to the ubiquity of rotavirus in Bangladesh (ICDDR,B 2003), and its hygiene-related mode of transmission, it was assumed that those older than one year were immune and then remain immune due to repeated asymptomatic re-infection and exposure. Therefore, a susceptible fraction in the general population of only 1.6% (based on life expectancy of 62 years), tenfold lower than the 17% proposed by Havelaar & Melse (2003), was adopted as being more realistic. For the protozoal and bacterial reference pathogens, the assumptions on background immunity of Havelaar & Melse (2003) based on developed world data were arbitrarily reduced by

ten-fold to give a susceptible fraction of 7.1% and 9%, respectively. This ten-fold difference may be reasonable given, for example, that bacterial pathogens are uncommon in developed countries but are routinely isolated in Bangladesh in around 10% of hospitalised patients whose stools are sampled regardless of condition (ICDDR,B 2003). The same analysis reveals rotaviral isolation frequencies around ten-fold higher than reasonably comparable developed world analyses (e.g. Hellard *et al.* 2001 compared with ICDDR,B 2003).

The probability of death per symptomatic case, the case fatality ration (CFR), for the viral and bacterial pathogens were set at 0.23%, a figure based on the 1991 BBS census for hospitalised deaths from diarrhoea in which of 1,250 deaths were observed in 532,031 hospitalised diarrhoeal cases. The hospitalised are the more serious cases making this CFR a possible over-estimate. On the other hand, once hospitalised, interventions will reduce the probability of death compared with that faced by cases remaining in the community, leading to a potential under-estimate of the true CFR. These two factors may balance out and 0.23% is reasonably consistent with the 0.6% CFR estimated by Havelaar & Melse (2003) for the developing world. The generally less severe (in the immuno-competent) protozoan pathogens were assumed to be less fatal and a CFR of 0.01% was applied (Havelaar & Melse 2003 citing Hunter & Syed 2001).

In summary, the DALYs per reference pathogen microbial infection applied in the present study were 2.4×10^{-3} for virus, 1.3×10^{-2} for bacterium and 1.4×10^{-4} for protozoan. The DALYs per case of arsenic related cancer applied in the present study were 1.18 for skin cancer, 16.29 for lung cancer and 13.67 for bladder cancer as described by Havelaar & Melse (2003), after adjusting for a reduced life expectancy at birth.

RESULTS

Water quality data from 36 individual water supplies each from dug wells and deep tubewells and 24 shallow tubewells from 12 clusters were collected, along with 42 water supplies each from rainwater harvesting and pond sand filters from 14 clusters in both dry and monsoon conditions (Ahmed *et al.* 2005) between September 2004 and June 2005. In most cases the majority of results were above the limit of quantification or limit of detection of the assay used. However, more than half of the microbial concentrations in deep tubewells were below the assay detection limit (1 per 100 ml) and although log normal distributions could be fitted to the observed data, there would necessarily be a reduced level of confidence in the extent to which the fitted distribution represented the true microbial concentration.

Disease burden estimates for the technology options assessed are illustrated in Figure 2. The level of uncertainty (for model assumptions) and variability (from the monitoring data) in the estimates was found to be high with the 90% confidence intervals spanning more than one order of magnitude for most assessments and overlapping between technology options. Overall the data show that dug wells and pond sand filters represent a generally much higher risk than deep tubewells or rainwater. It should also be noted that a significant number of rainwater harvesting schemes and pond sand filters were non-functional during the dry season.

Viral and bacterial pathogen concentrations dominated the disease burden estimates for the microbial DALY results with protozoal risks contributing relatively negligible risks to the total (Figure 3a). At the lower TTC concentrations ($\leq$244 cfu) the viral disease burden was the most significant contributor and at higher TTC concentrations ($\geq$245) the bacterial disease burden began to dominate as the viral disease burden reached its saturation point.

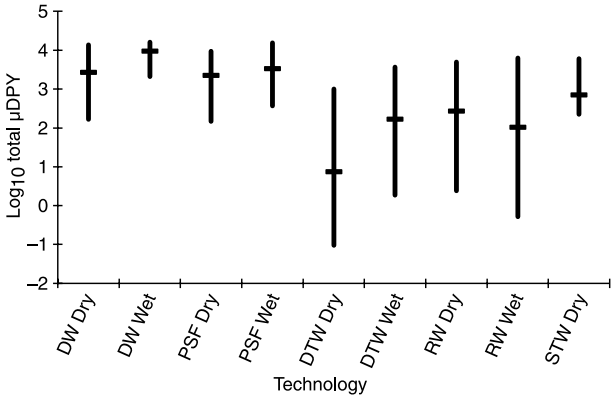

Figure 2 | Summed DALYs predicted from the analysis of thermotolerant coliform and arsenic data from the RAAMO survey. Results are log 10 µDALYs per person-year (µDPY) additional disease burden due to the water supply option in wet or dry season and for dug well (DW), shallow tube well (STW), deep tube well (DTW), pond sand filter (PSF) and rainwater harvesting system (RW). Horizontal bars: median; vertical bars: 90% confidence interval.

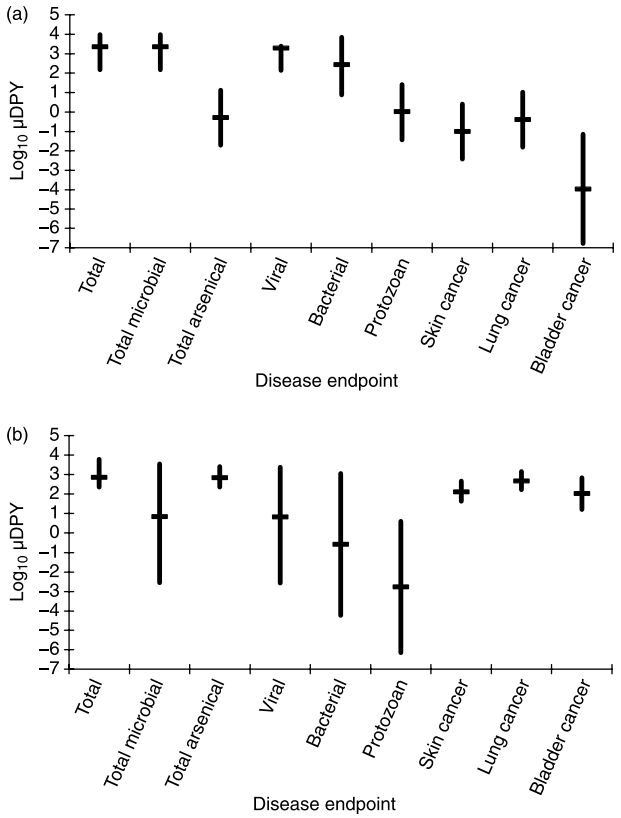

Figure 3 | Illustration of disease burdens predicted to be associated with (a) pond sand filter in dry season and (b) shallow tube well in dry season. Results are log10 μDALY per person·year (μDPY) additional disease burden shown for each predicted endpoint. Horizontal bars: median; vertical bars: 90% confidence intervals. Input values for the model were obtained from the RAAMO survey as shown in Table 2.

Skin cancer and lung cancer dominated the predicted arsenic disease burden (Figure 3b); lung cancer was predicted to be a greater contributor than skin cancer across the dynamic range of the study. In general, microbial disease burdens were predicted to be a greater proportion of the total DALYs attributed to each technology option under each weather condition with the exception of the median DALY estimates for the shallow tubewell option in the dry season (Figure 3b), where the arsenic DALY was predicted to dominate. In general, the lowest risk arsenic mitigation options in terms of predicted disease burden were the deep tubewells and the rainwater harvesting systems although both were predicted to present a significant upper (95th percentile) microbial risk estimate if not appropriately maintained (Figure 2).

The level of dispersion in model assumptions was significant and is indicated numerically by the statistics shown in Table 2 and 3 and graphically in Figure 2 and 3. A large contributor to the overall breadth of the disease burden estimate confidence interval is the variability in observed TTC and arsenic monitoring results. The variability in the water quality performance of any one technology can be greater than the variability in the water quality performance between two different technologies given the effect of spatial, climatic and management factors.

DISCUSSION

It was assumed that all water said to be directly consumed in the Watanabe *et al.* (2004) study was unboiled as there were no indications to the contrary in the report, although this was not explicitly stated. This is not a criticism of the Watanabe *et al.* (2004) study, which was assessing water consumption for arsenic and not pathogen exposure such that boiling was not relevant to their analysis. However, in future assessments of water consumption, it would be useful to record not only direct consumption but also direct unboiled water consumption to enable the data to be more broadly used in microbial risk assessments.

Although not excessive compared with the results of many other risk assessments (e.g. Teunis *et al.* 1997), the magnitude of the uncertainty in the outcomes of the QHRA illustrates the need to interpret the results of QHRA in context. Proper consideration needs to be given to other factors, including evidence that cannot necessarily be captured in a simple spreadsheet model that is based on limited observations. The results of QHRA modelling should be considered as just one input to a decision-making process and should be interpreted by experienced water, sanitation and health sector professionals with sufficient local knowledge to make practical judgements.

Disease burdens estimated for bacterial and viral reference pathogens were the major contributors to the microbial risk assessment predictions. Therefore, further research to reduce the uncertainty in model outputs can most usefully be focused on factors that affect assumptions relating to these two reference pathogen classes. It would be interesting to attempt to validate this predicted relationship by examining microbial indicator concentrations to pathogen isolations to see if the ratio of bacterial to viral isolations increases with increasing indicator concentrations in the water used for drinking.

There is significant uncertainty surrounding the assumptions relating to the ratio of pathogens to *E. coli* and the ratio of TTC to *E. coli*. The proportion of TTC that are, in fact, of faecal origin is likely to be highly variable and a longitudinal study involving the typing of recovered TTC, or at least analysing for *E. coli* and TTC, would be desirable as a means of providing a basis for assessing the sanitary significance of TTC counts in Bangladesh. A move towards *E. coli* testing where reliable and practical is also warranted. Although kits currently exist for testing *E. coli* in the field, the costs generally preclude their routine use in testing rural water supplies in developing countries. The development and use of lower cost, affordable and reliable field kits that specifically test for *E. coli* could improve the targeting of public health interventions.

The ratio of [*E. coli*]:[pathogen] is one of the least supported components of the model and one of largest sources of anticipated error. The variables affecting pathogen fate, survival and transport have been reviewed in detail (Ferguson *et al.* 2003) and it should be possible to improve the validity of ratio estimates by modelling pathogen and *E. coli* fate and transport through the most plausible scenarios by which microbial contamination might arise for each technology. For example, birds are more likely to contribute to rainwater providing a basis for raising the [*E. coli*]:[virus] and [*E. coli*]:[protozoan] ratios. Similarly, dry season contamination is more likely to be subsurface, providing a basis for lowering [*E. coli*]:[virus] and raising [*E. coli*]:[protozoan] ratios. Such modifications can readily be made within the modelling framework applied.

The overlap in the predicted disease burdens between technologies and the broad range of TTC and arsenic results observed for each technology illustrate that poorly managed or implemented water supply systems, even if theoretically capable of providing good water quality, are likely to yield poor water quality under failure mode operating conditions. This finding supports the emphasis of the World Health Organization on the Water Safety Plan approach (WHO 2004; Davison *et al.* 2005) in which rigorous water quality risk management plans are implemented to protect drinking water quality consistently.

The 3rd edition of the Guidelines for Drinking Water Quality (WHO 2004) recommends a reference level of risk per contaminant of 10^{-6} DALYs per person·year (1 μDPY). For bacterial pathogens, only the median quality of deep tubewells in the dry season approached this level and most technologies in most seasons were significantly higher than this level. Dug wells and pond sand filters in particular showed much greater health risks. The health risks from pathogens for rainwater increased in the dry season; however, the source of the increased microbial contamination warrants further investigation to assess whether this is a realistic estimate. If the increased contamination derives from the washing in of faecal matter in the periodic storms that occur in the late dry season, the increase in risk is justified. If the increased contamination derives from regrowth, the risk from diarrhoeal disease would be negligible (Hunter 2003). It is likely that further recontamination occurs during transport and storage, which will further increase the risk (Howard *et al.* 2006).

None of the water supply options, when all DALYs were summed, met the 1 μDPY WHO reference level of risk on a sustainable basis. It should be noted, however, that the 1 μDPY WHO reference level relates to risk per contaminant. Water supplies containing many contaminants at their guideline values would very plausibly present a disease burden in excess of 1 μDPY.

Although the outcomes of this QHRA are uncertain, the results are consistent with one of the findings from the study of Lokuge *et al.* (2004). Caution needs to be exercised in introducing arsenic mitigation options to ensure that disease burdens are not increased by this act (Howard 2003). In particular, some of the highest risk mitigation options would plausibly lead to disease burdens considerably higher than those presented by shallow tubewells that contained arsenic at concentrations just above the Government of Bangladesh guideline value of 50 $\mu g\,l^{-1}$. For example, the disease burden presented by a water supply with arsenic at 50 $\mu g\,l^{-1}$ was a median of 185 μDPY. The same total disease burden was predicted to be presented by pathogens once thermotolerant coliforms exceeded their guideline value of <1 cfu 100 ml^{-1}. Specifically, a 185 μDPY disease burden was exceeded once the median thermotolerant coliform concentration was above >1.4 cfu 100 ml^{-1}).

CONCLUSIONS

The disease estimation tool has proved to be a useful way of comparing the potential disease burden associated with

different water supply options and to inform technology choice. The data from the RAAMO studies suggest that deep tubewells and rainwater harvesting show the lowest disease burden, although not all rainwater systems function in the dry season. Dug wells and pond sand filters represent a higher risk and probably require chlorination.

The model showed that QHRA is possible in environments with limited data and can be expanded to include chemical as well as microbial hazards. The predominance of viral and bacterial pathogens accords well with available epidemiological data. The importance of viral pathogens from water raises important questions, given the well-documented hygiene and sanitation influence. It is likely, however, that viral disease burdens from water in developing countries have historically been under-estimated as most clinical data was derived for bacterial pathogens. The end-points for arsenic are also limited by available epidemiological data and the model should be refined as new data become available.

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