

# An answer to **arsenic**

**Dr Maitreyi Mazumdar** discusses her deep connection with Bangladesh and how her work aims to improve public health there in response to the epidemic of arsenic poisoning



## What is your research background, and how did you come to establish environmental health projects in Bangladesh?

I am a paediatric neurologist and an epidemiologist. I spent the early years of my medical training completing a residency in general paediatrics, and then subsequently pursued specialised training in child neurology. Clinical care is focused on doing one's best for an individual patient, but as my clinical training ended, I realised that I also wanted to become involved in improving the health of populations. Specifically, I wanted to understand why certain groups of people were more likely to develop neurological diseases, and I wanted to learn how these diseases could be prevented. I therefore completed a master's degree in Epidemiology at the Harvard School of Public Health. It was there that I joined a research team with a long history of productive collaboration in Bangladesh, and was studying the health consequences of the arsenic poisoning epidemic in this country. Their studies had focused primarily on adults, but as they were turning

their focus to children, I was recruited to train doctors to perform standardised neurological examinations and neurodevelopmental assessments. This initial work then led to many more projects in Bangladesh.

## A key facet of your work has been your close association with Bangladeshi culture. Could you elaborate on this?

My father's family lived in what is now Bangladesh, and my great-grandfather was the first dean of the law school at Dhaka University in the 1920s. My parents grew up in Kolkata, India, and moved to the US in the early 1960s with my older brother. My twin brother and I were born in the US. At that time, there were not many opportunities to travel to India and Bangladesh, but we learnt much about the language and culture through our parents and their friends. As we have grown older, and travel has become easier, we've been able to travel to Bangladesh frequently. My twin brother was recently posted in the US Embassy in Dhaka as a US Foreign Service Officer.

## Why is arsenic poisoning such a widespread problem in this region?

Exposure to arsenic through drinking water sources is a global public health emergency, and this epidemic is particularly devastating in Bangladesh. According to survey data from 2000-10, an estimated 35-77 million people in the country have been chronically exposed to arsenic in their drinking water. This situation has been described by the World Health Organization (WHO) as the largest mass poisoning of a population in the world's history, and it stems from the 1970s, when millions of wells were dug in rural areas of Bangladesh in an effort to reduce transmission of cholera and other enteric diseases via pathogen-laden surface waters. It wasn't until decades later,

when the people who had been drinking this water began to present with signs of arsenic toxicity, that it was realised that this water was contaminated with naturally occurring arsenic.

## How does your work on arsenic exposure relate to cystic fibrosis research?

Cystic fibrosis a rare autosomal recessive disease most common in people of North European ancestry. The genetic mutations responsible for most cases of cystic fibrosis are not found in Bangladesh. However, arsenic toxicity is associated with lung infections and diabetes – symptoms that overlap with cystic fibrosis. We have recently shown that elevated sweat chloride concentrations (the diagnostic hallmark of the disease) are found among adults with high levels of arsenic exposure through drinking water. This finding is significant because it shows that an environmental hazard can mimic, even at the most basic biochemical level, a genetic disease. It is also significant because it elucidates a potential biological mechanism for arsenic toxicity in humans – that is, degradation of the chloride channel that is improperly formed in people who have cystic fibrosis. This finding opens up many new fields of research, as therapies that have been developed for these patients may prove to be effective in treating arsenic toxicity. In the same manner, understanding arsenic toxicity might benefit the development of treatments for cystic fibrosis.

## To what extent is your team's research a multidisciplinary endeavour?

Our group works with statisticians, chemists, physicians, engineers, public health practitioners, basic neurobiologists and many others. Collaborating with these professionals with very different backgrounds and making connections across disciplines are in fact some of the most satisfying parts of my job.





# Tube wells and **neural tube** defects

A **Harvard School of Public Health** research group is elucidating the health consequences for children of the arsenic epidemic and the molecular mechanisms that underlie these effects through a series of ambitious epidemiological studies

**THE EPITHET 'NATURAL'** is widely applied to imply high quality and often health benefits – but natural certainly does not always mean healthy. Indeed, for almost nine out of 10 people in Bangladesh, one naturally occurring chemical present in their drinking water has been responsible for some devastating health consequences.

The culprit is arsenic. This notoriously toxic chemical has been seeping into Bangladesh's underground aquifers for decades. Although tube wells have been pumping groundwater to the surface since the 1940s, their use exploded over the 1970s and 1980s when the United Nations Children's Fund (UNICEF) and others championed their instalment as a means to reduce incidence of enteric illnesses caused by drinking pathogen-laden surface water. It has only been in recent years, as the health effects of long-term arsenic poisoning have been observed in the general population, that it was realised that these tube wells are bringing more than groundwater to the surface.

Now, the situation is stark; the World Health Organization (WHO) estimates that, in recent decades, up to 61.6 per cent of Bangladeshis may have been exposed to toxic arsenic levels. An environmental health disaster of this scale is, quite simply, unprecedented.

## THINK OF THE CHILDREN

For the younger generation of Bangladeshis, the future health impacts of this situation are uncertain, as research into the effects of early arsenic exposure on development and long-term health is limited. One group of researchers aiming to fill this knowledge gap, however, can be found at the Harvard School of Public Health (HSPH) in the USA. Recently joined by paediatric neurologist and epidemiologist Dr Maitreyi Mazumdar, the HSPH team has been conducting research on the health impacts of the Bangladeshi arsenic poisoning epidemic for years, both in adults and, more recently, in children. "Our underlying methodology is to use population-based study designs to translate findings in animal studies/experimental models into human populations," elaborates Mazumdar.

To aid them in their fieldwork, the researchers have multiple longstanding links with local collaborators in Bangladesh, and also benefit from Mazumdar's knowledge of the local language and culture, which was instilled in her during childhood owing to her family's roots in neighbouring areas of India. Understanding and adapting to cultural context is a vital component to the team's work. "One of the first tasks I undertook when starting to work in Bangladesh was adapting a neurodevelopmental assessment tool that includes pictures. This tool prompted children to talk so that, as assessors, we

could evaluate their use of language," Mazumdar recalls. "The pictures were of snowmen, scarves, apples... It would have been naive to think that this instrument would work in Bangladesh."

## ARSENIC AND NEURAL TUBE DEFECTS

Neural tube defects are the second most common severe disabling birth defect in the world. They occur as a result of improper formation of the neural tube (the embryonic precursor of the brain and spinal cord) as a result of genetic, nutritional and/or environmental factors. Although the significant role played by folic acid deficiency in the development of neural tube defects is widely recognised – hence the prominence of health guidelines recommending women take folic acid supplements when trying to conceive and throughout early pregnancy – animal models and experimental systems have also suggested that arsenic exposure may contribute to neural tube defect development.

Mazumdar decided to investigate the potential link between maternal arsenic exposure and neural tube defect development. To achieve this, she and her collaborators first had to establish a birth defect ascertainment system in the field, as Bangladesh had no such surveillance programme in place. This is a feat that Mazumdar counts among her proudest achievements. "It really will change lives if we can demonstrate that there is

## Mixed menaces

Children in poverty face many forms of adversity that can disrupt brain development, from harmful chemical exposure to micronutrient deficiencies. Dr Maitreyi Mazumdar is using her studies in Bangladesh, in combination with others from around the world, to develop an easy-to-use scoring system that will identify children at the highest risk of cognitive impairment.

### PROJECT 1: EPIDEMIOLOGY OF METAL MIXTURES AND NEURODEVELOPMENT

The longitudinal, population-based project is investigating the toxicity of lead, arsenic and manganese (and their mixtures) on the neurodevelopment of 2,600 children, by measuring infant neurodevelopment against levels and timing of mixed metal exposures. The researchers hope that their findings will contribute to the development of effective public health policies and interventions.

a population at extremely high risk who might benefit from targeted interventions," she states.

After enrolling 57 children affected by the neural tube defect myelomeningocele, alongside a group of controls, the team was able to conduct its analysis. The findings were significant: "Our preliminary results suggest that arsenic interferes with folic acid supplementation, the main strategy for preventing birth defects. This means that folic acid supplementation might be less effective in areas with high levels of arsenic exposure," Mazumdar reveals. Further investigations are now underway to determine the mechanisms by which this interaction or interference may occur, via a larger population-based case control study in Bangladesh that aims to assess the relationship between environmental arsenic exposure and neural tube defects while also analysing genetic and nutritional factors that may influence individual arsenic sensitivity. "It may be that arsenic uses up the available folate needed for normal neural tube development, or there may be another mechanism – perhaps epigenetic – at play," Mazumdar speculates.

### A RENEWED FOCUS ON LEAD EXPOSURE

With projects such as this in the pipeline, Mazumdar's research group looks set to make significant contributions to public health in Bangladesh, as well as further afield, because the knowledge the team generates has relevant applications wherever toxic metals are present. The group's next project, for example, will focus on quantifying the relative contribution of environmental hazards to children's cognitive development in developing countries, with a particular emphasis on lead poisoning. This work means that more resources can be directed towards safeguarding these nations' youngest citizens – efforts that could be translated across any number of different regions and contexts. For the moment, however, Mazumdar has no plans to end her work in Bangladesh. "This work is very important for millions of children," she states simply.

### PROJECT 2: EARLY IDENTIFICATION OF INFANTS AND YOUNG CHILDREN AT INCREASED RISK OF COGNITIVE IMPAIRMENT

This project involves building a predictive model that identifies important variables from the Bangladesh study that correlate with cognitive development. This model will be tested and validated using longitudinal cohorts in other settings. The goal of this scoring system is to identify which variables and laboratory tests should be included in routine developmental screening tests for low-resource settings.



### Toxic turmeric

Mazumdar and her collaborators were instrumental in helping to identify contaminated turmeric as a source of lead exposure for rural Bangladeshi children. This finding emerged as a result of a cohort study investigating the associations between mixed metal exposures and child health outcomes, during which 78 per cent of children evaluated were found to have blood lead concentrations above current US Centers for Disease Control and Prevention (CDC) reference levels. Home visits and inspection of local businesses established turmeric as a potential source of childhood lead exposure – possibly as a side effect of artificial colouring.

## INTELLIGENCE

### HAZARDOUS ENVIRONMENTAL EXPOSURES AND NEUROLOGICAL DEVELOPMENT OF BANGLADESHI CHILDREN

#### OBJECTIVES

- To undertake a large-scale epidemiological study in Bangladesh that investigates the effects of arsenic and toxic metals on the cognitive development of children
- To ascertain whether arsenic exposure is contributing to an epidemic of neural tube defects in Bangladesh
- To understand the relative contribution of hazardous environmental exposures, in particular lead poisoning, to cognitive impairment of children in developing world settings

#### KEY COLLABORATORS

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