



# Global Health Threats Monitor

## CONTENTS

This week's news

Avian Flu Update

Disease Outbreaks Update

## THIS WEEK'S NEWS

Rice is a major source of arsenic exposure in West Bengal

New addition to the *Bartonella* bugs

Cheap, effective meningitis vaccine close

How to know if the chemicals will go

Modelling immune response may provide clues to treatments

## Rice is a major source of arsenic exposure in West Bengal

*Arsenic does not only contaminate water, warn environmental scientists, and policy makers should take note*

Rice can make up to 70–80% of the total cancer risk from arsenic for people living in West Bengal, researchers revealed last week at the European Conference of the Society for Environmental Geochemistry and Health.

“The arsenic calamity in West Bengal is now considered as one of the biggest mass poisonings in the world, just behind the one in Bangladesh,” said presenter Debapriya Mondal of the University of Manchester, UK. More than 50 million people are living in arsenic-affected districts there, and 7 million people are drinking contaminated water above the Indian limit of 50 µg/l — the World Health Organization limit is 10 µg/l.

Arsenic is well known as a cause of lung, bladder, kidney, stomach, and skin cancers, but can also lead to diabetes mellitus, hypertension, cardiovascular diseases, adverse reproductive outcomes, neurological effects, and skin lesions. According to a UN report 1.7 million people from West Bengal have arsenic-related diseases, but it could be up to 3 million, other research groups suggest.

The epidemiological studies in the region have assumed drinking water is the exposure route for arsenic in this region. “Considering only drinking water as an exposure route leads to the neglect of the additional exposure from food,” Mondal cautioned.

She and her supervisor David Polya looked at the contribution of rice to overall exposure. Rice grown on arsenic-contaminated soil and irrigated with arsenic-contaminated groundwater accumulates the toxin to high levels, and people in West Bengal eat a lot of rice — 73% of the calorific value in an average diet comes from rice. Other vegetables also



Our Sponsors



*“The arsenic calamity in West Bengal is now considered as one of the biggest mass poisonings in the world, just behind the one in Bangladesh.”*

*Debapriya Mondal,  
University of  
Manchester, UK*

have high arsenic, but people eat comparatively few of them. Whether arsenic in rice is truly a danger to the people who eat it is still under debate.

Mondal and Polya decided to determine the overall increase in cancer risk due to arsenic-contaminated rice in two typical arsenic-bearing regions in West Bengal to see whether eating rice is a significant route of exposure for the people living there.

They chose two districts, North 24 Parganas and Nadia, where they sampled the rice in several villages with high arsenic levels, and calculated the lifetime risk to the people eating it. They took into account the bioavailability of the arsenic in the rice; that is, how much of the toxic form of arsenic would be likely to be absorbed by the gut during digestion. They also accounted for average rice ingestion rate, and normal population characteristics like age, weight, and life expectancy from WHO statistics.

Uncooked, the rice had about 230 µg/kg of arsenic and this equated to an additional risk of cancer from rice of around 1:1000, at least an order of magnitude greater than the US EPA carcinogenic risk limit of 1:10,000 to 1:1,000,000. Eating rice accounted for 70–80% of the total risk from arsenic, if the people were drinking water with 10 µg/l arsenic (which is the case in some places where it is treated), or 30–40% of the total risk if the drinking water has 50 µg/l arsenic.

“What we can say is that rice is the most significant route of exposure in groups exposed to low or no arsenic in drinking water,” Mondal concluded. “This is an important finding for policy makers since considering only exposure in water, and having mitigation in place to take care only of that, might lead them to neglect the exposure from food.” This region grows rice that is distributed to the rest of the country, she pointed out.

The figures match well with research coming out of Bangladesh, according to Andrew Meharg, Professor of Biogeochemistry at the University of Aberdeen, who has looked at arsenic levels in rice in Bangladesh, Europe, and the USA. That there is a problem with arsenic in rice grown on arsenic-rich soil or using arsenic-laden water is increasingly being recognised, he says.

His group are looking for rice varieties that will accumulate less arsenic from the soil, as small-scale ‘pot experiments’ show there is some variation in the ability of different cultivars to take up arsenic. The next step will be to test some of the least arsenic-accumulating varieties out in the field, with the idea of introducing those in arsenic-rich areas. “That to me is the only feasible mitigation strategy,” said Meharg. “The soil is already contaminated, you can’t get rid of the contamination easily, and people aren’t going to stop using the groundwater to irrigate dry-season rice.”

“Meticulous bedside-to-bench research like that conducted by Eremeeva et al. is vital to the discovery of new or previously unrecognised infectious diseases.”

Gary Wormers,  
Division of Infectious  
Diseases, New York  
Medical College, New  
York, USA

## **New addition to the *Bartonella* bugs**

*Pathogenic species of bacterium discovered in blood of patient who recently travelled in Peru*

Cat-scratch fever, trench fever, Oroya fever: the evocative names of some of the serious infections caused globally by *Bartonella* bacteria. The *Bartonella* species known to be pathogenic to humans now number four, with the report of a new family member — *Bartonella rochlimae* — in the *New England Journal of Medicine*.

The bugs were recovered from the blood of a patient with fever, headache, nausea, and enlarged spleen who had been bitten by unknown insects during her recent stay in Peru. The symptoms were very similar to Oroya fever, an infection endemic in the Andes caused by *Bartonella bacilliformis*.

Treatment with antibiotics cleared up the symptoms, and it would have been easy to have let the matter rest there. However, Marina Eremeeva and colleagues cultured the patient’s blood to see what the precise cause was. Microbiological, immunological, and genetic analysis revealed a previously unknown species related to *B. bacilliformis*.

Quite how much of a problem this bacterium is causing for people is unknown as this is the only infection identified so far. The authors speculate that because of the similarity in symptoms, some cases reported as Oroya fever could in fact be due to *B. rochlimae*.

How the bug got into the patient hasn’t been pinned down either. However, *B. bacilliformis* and another *Bartonella* species, *B. quitana* (the cause of trench fever), are transmitted through insect bites. Eremeeva and colleagues’ genetic analysis turned up a piece of DNA that is extremely similar to one found in a pulex flea from Peru, so this could be a possible vector for the bacterium.

“This case illustrates the importance of culturing specimens from patients to test for *Bartonella* species... and remaining vigilant for new *Bartonella* species that are pathogenic in humans,” the authors conclude.

Gary Wormers, of the Division of Infectious Diseases at New York Medical College agrees. “[The patient] would have been given a diagnosis of Oroya fever had these investigators been less conscientious about precisely identifying the bacterium recovered from her blood,” he writes in an accompanying article. “Meticulous bedside-to-bench research like that conducted by Eremeeva *et al.* is vital to the discovery of new or previously unrecognised infectious diseases.”

---

## **Cheap, effective meningitis vaccine close**

*Successful Phase 2 clinical trial provides hope of ending African epidemics “in the next few years”*

Preliminary results are now in from a clinical trial of a vaccine against serogroup A *Neisseria meningitidis*, the cause of epidemics

*“When it becomes part of the public health arsenal, this vaccine will make a real difference in Africa.”*

*F. Marc LaForce,  
Director of the  
Meningitis Vaccine  
Project*

in the notorious ‘meningitis belt’ in sub-Saharan Africa. The vaccine is safe and much more effective than any other available in the region, the Meningitis Vaccine Project announced today. If all continues well with further testing, the jab could be introduced for mass immunisation within three years at a cost of 40 cents (US) a dose, they say.

“When it becomes part of the public health arsenal, this vaccine will make a real difference in Africa,” said F. Marc LaForce, director of the Meningitis Vaccine Project, a partnership between the World Health Organization and the not-for-profit group PATH. “Elimination of these epidemics with wide use of the meningococcal A conjugate vaccine is now a likely possibility over the next few years.”

The African meningitis belt extends from Senegal and The Gambia in the west to Ethiopia in the east, with a population of about 430 million being at risk for the sporadic outbreaks of the disease. In 1996–97, the largest recorded epidemic caused more than a quarter of a million cases and 25,000 deaths across the region. And, with 41,526 cases last year and the 47,925 cases reported already this year (to 6 May) concern is growing that another epidemic is ready to sweep across the belt.

The vaccine was tested in 600 12- to 23-month-old toddlers in Mali and The Gambia. It produced almost 20 times the antibodies against *N. meningitides* than those elicited by the currently available vaccine, suggesting that it will protect against the disease for several years.

“This important study brings real hope that the lives of thousands of children, teenagers, and young adults will be saved by immunisation and that widespread suffering, sickness and socio-economic disruption can be avoided,” said WHO Director-General Margaret Chan.

The Meningitis Vaccine Project and the vaccine’s makers, Serum Institute of India, now plan a Phase 2/3 trial in two- to 29-year-olds in Mali, The Gambia, and at least one other African country. Another study is scheduled in India, where the vaccine will be licensed.

---

## **How to know if the chemicals will go**

*Software that tries to predict whether a compound will be degraded by microbes in the environment highlights the complexity of the problem*

The number of new chemicals being manufactured has rocketed recently, far outstripping experimental attempts to determine what might happen to them if they were released into the environment. In the absence of hard data, Manuel Gómez and colleagues have turned to computer modelling to predict whether a compound is likely to be broken down by bacteria in the environment.

*"[A model] can never be better than the data."*

*Jirí Damborský,  
National Centre  
for Biomolecular  
Research, Masaryk  
University, Brno,  
Czech Republic*

"The production of new chemicals for industrial or therapeutic applications exceeds our ability to generate experimental data on their biological fate once they are released into the environment," explain Gómez and colleagues in *Molecular Systems Biology*. "Knowing whether a novel chemical compound is likely to be metabolised by microorganisms is crucial for assessing the environmental risks associated with its production, transportation, utilisation, and disposal."

The team started with experimental data from two public databases of information about how several hundred different chemicals are broken down by environmental microbes, the University of Minnesota Biodegradation and Biocatalysis Database and the Biodegradative Strain Database of Michigan State University. The authors described each of the chemicals with an atomic triad notation, where every group of three consecutive connecting atoms in the molecule is denoted.

With these defined compounds, Gómez and colleagues used a machine learning system to 'train' software to recognise which compounds are biodegradable based on their constituent triads, and their molecular weight and water solubility. The software linked certain triads with biodegradability and others with non-biodegradability. The team then employed the final program (called BDPServer) to predict the fate of several sets of compounds for which there are no biodegradation data, highlighting herbicides as particularly resistant to being broken down by microbes.

Predicting biodegradability has always been difficult because of the complexity of the problem, according to Jirí Damborský of the National Centre for Biomolecular Research at Masaryk University, Brno, Czech Republic. Biodegradability depends not only on the chemical's structure but a myriad of other factors: environmental conditions such as pH, concentrations of the chemical, the microbial species present, what other compounds there are, and so on, he points out. Moreover, the value of any model will depend on the data used to develop it. "[A model] can never be better than the data," Damborský says.

Other predictive systems have, however, used the same data as Gómez and colleagues to come up with very different answers, points out Larry Wackett, Professor of Biochemistry at the University of Minnesota. He is one of the creators of the University's Biocatalysis/Biodegradation Database and his team has developed another prediction program, the Pathway Prediction System. "We use functional groups [instead of atomic triads], as these are the units of reactivity in chemistry and biochemistry (at the active sites of enzymes)," he says. "The system discussed in the paper finds many herbicides/pesticides to be non-biodegradable. The Pathway Prediction System finds virtually all of them to be biodegradable and predicts one or more biodegradation pathways."

With the value of the different systems still under discussion, computer predictions can not be used to replace experimental testing, Damborský cautions. However, they can be useful, for example, in setting priorities for testing. Also, having some sort of information, even if it is debatable, will appeal to decision-makers who do not have immediate access to laboratory data.

The authors agree. They foresee that the tightening of chemicals regulations in the EU (REACH) and elsewhere (e.g. the US Pollution Prevention Framework) could mean that prediction programs such as theirs will increasingly be used as a starting point for determining the potential fate of chemicals in the environment. “We expect predictive approaches [like ours] to inform decisions about acceptability of the release of current and future chemicals into the environment,” they say.

## Modelling immune response may provide clues to treatments

*Simulation of host–pathogen interactions answers questions before costly experiments are needed*

Pathogens often manipulate the pathways responsible for immune responses in the host they’ve infected. To understand these pathogenic systems and be able to block them, key components and regulatory interactions need to be known. Juilee Thakar and colleagues, from Pennsylvania State University, mapped out a comprehensive network model of interactions between two pathogens and the host immune systems. They hope to use the model to address questions that have yet to be tested experimentally and provide reasoned answers, saving expensive and time-consuming animal experiments.

Thakar *et al.* chose two closely related species of *Bordetella* to examine as these bacteria successfully overcome host immune responses, their genomes are sequenced, and they provide a comparative model. These small Gram-negative coccobacilli cause whooping cough in humans (*B. pertussis*) and kennel cough in dogs, as well as infecting other animals, such as pigs, cows, and rabbits (*B. bronchoseptica*).

The major aspects of *Bordetella* virulence and host immune response have been studied in the past 20 years. Thakar and colleagues’ used these data, along with their own experimental data, and putative interactions based on general immunology to draw up an interaction network. The map shows bacteria and immune system components (immune cells and cytokine molecules) as nodes and their interactions as lines between them from source to target node. The resultant map had 18 common nodes and two species-specific nodes.

“Our methodology can be extended to other respiratory pathogens and ultimately to pathogens in general.”

Juilee Thakar,  
Pennsylvania State  
University, USA

Next, dynamic information was entered into the model. Information on the time-dependent expression of specific virulence factors and immune components from the literature was added to create a time frame for the simulation. Discrete steps cause status changes in the nodes using Boolean transfer functions (AND, OR, NOT, etc.), depending on the status of nodes that regulate them. The model was run 1000 times from the basic assumption of a previously uninfected host encountering bacteria; all nodes were off (0) except for the bacteria, which was on (1).

Three common phases of infection were identified by the simulations: innate responses; B-cell and antibody-mediated responses; and Th1-related responses, leading to phagocyte recruitment and activation, and thus to bacterial clearance. These three stages were supported by experimental data. Various scenarios were then modelled by turning off certain nodes and observing the effects in 1000 simulations. Such models included deleting bacterial virulence factors, deleting elements of the immune system, treatment with antibodies, modelling a re-infection with the same bacteria, and cross-infection with related species. The models' predictions were validated experimentally in genetically engineered mice lacking certain immune system elements, and in secondary infection.

Modelling such as this has been used to predict the dynamic trajectory of biological systems using gene regulatory and signal transduction networks, say the authors. The benefits of such a model in immunological systems, they believe, are that it will allow researchers to see knowledge gaps and allow identification of new relationships. The model can predict the outcome of perturbations not yet explored experimentally, and thus direct future research efforts.

Thakar and colleagues posit that because the modelling of the initial stage of infection with deleted virulence factors resulted in earlier clearance of the infection, their system ultimately has the ability to predict which factors could be best targeted to promote recovery and influence the design of treatments for *B. pertussis*. "Our methodology can be extended to other respiratory pathogens and ultimately to pathogens in general," they conclude.

---

## AVIAN FLU UPDATE

### Confirmed death in China

The Ministry of Health in China confirmed the country's 16th death from H5N1 avian influenza to the WHO on 4 June. The 19-year-old male soldier serving in Fujian province died the day before. Of the 25 laboratory-confirmed cases in China since 2003, 16 have been fatal.

### Deaths reach 15 in Egypt

The Egyptian Health Ministry announced the death of a 10-year-old girl on 9 June from infection with H5N1 avian influenza, bringing the number of fatalities from the disease in Egypt to 15 since 2003. The girl fell ill on 1 June after coming into contact with infected household

birds. From the southern town of Qena, she was admitted to hospital on 7 June with a high fever and a pulmonary infection, and was put on an artificial respirator.

Her death followed a nearly two-month warm-weather lull in human avian influenza cases in Egypt. Avian influenza experts in Egypt said they would typically expect fewer human cases of the disease during Egypt's hot summer months; in 2006 there was a summertime lull in human cases between May and October.

## **Further outbreak of H2N7 in UK**

Despite health officials saying that the outbreak of the low pathogenic H2N7 avian influenza, which affected 17 people in north Wales, has ended, a restriction zone has been placed around a smallholding near St Helens, Lancashire.

The first case was found last month in poultry on a smallholding near Cerrigydrudion, Conwy. Some of the infected chickens in the latest outbreak had been bought from a market held in Chelford that was associated with outbreak in north Wales.

Two people who live on the smallholding were tested for the disease after exhibiting flu-like symptoms but the results were negative.

## **DISEASE OUTBREAKS UPDATE**

## **Singapore on brink of dengue epidemic**

Dengue infections in Singapore have risen to the year's highest reported in one week. A fortnight ago, 259 infections with dengue were reported, surpassing the warning level of 256 set by the Health Ministry. Epidemic levels are reached when more than 378 cases are reported in a week and health officials remain concerned about that possibility occurring soon.

There has also been a serious dengue outbreak in Myanmar, close to the Thai border. A hospital in the town of Three Pagodas Pass has been treating about 70 patients a day since mid-May, with 10 children reported to have died so far.

Across the Thai border, a hill-tribe village in Chiang Rai has about 5% of its 2000 residents infected this year. These outbreaks follow the news from Malaysia reported in late May of a 100% increase in deaths from dengue fever compared with figures from 2006.

Global Health Threats Monitor © Forum for Global Health Protection 2007

The Forum for Global Health Protection is an independent, not-for-profit association established with support from the UK's Health Protection Agency. It provides research-based information for scientists, public health policymakers, and the international business community. The Forum's service online includes news, reviews, and peer-reviewed research, available on an open-access basis.