



Global Health Threats Monitor

CONTENTS

This week's news

Avian Flu Update

Disease Outbreaks Update

THIS WEEK'S NEWS

Thai dengue burden ranks higher than thought

Emergence of XDR-TB in Europe blamed on mismanagement

Safety trial of bird-flu vaccine positive

The trick to taking over

Super-absorbent gels to mop up solvents

Watching bugs clean up

Thai dengue burden ranks higher than thought

Disease has been under-reported, say infectious disease specialists

A prospective five-year survey of fevers suffered by 2119 children at a primary school in Thailand is published in this week's *Lancet*. The analysis calculates the mean burden of dengue illness in the cohort to be 465.3 disability-adjusted life years (DALYs) per million per year. This puts it 12th on the burden list of infectious diseases in the region, above hepatitis C and intestinal nematode infections, and two places higher than a previous WHO estimate. "These data should represent the full burden of dengue illness in the cohort," write authors Katie Anderson and colleagues.

Dengue infection has spread rapidly since its identification from epidemics in the Philippines and Thailand in the 1950s. It is now endemic in more than 100 countries, with Southeast Asia and the Western Pacific being most seriously affected. Almost two-fifths of the world's population are now at risk from the infection, and the WHO estimates that there could be as many as 50 million cases of dengue infection worldwide every year.

Data on the actual number of cases is sparse because, although dengue is generally a notifiable disease in areas where it is endemic, this practice is rarely enforced. "Under-reporting is usually the most important challenge to obtaining reliable national estimates



The dengue virus is mainly transmitted by *Aedes aegypti* mosquitoes, a species found living in close association with humans in most tropical urban areas.

(Source: CDC/James Gathany)



Our Sponsors



“Quantification of [disease] burdens is crucial to the formulation by governments, donors, and industry of decisions for the prevention and management of dengue.”

*Scott Halstead,
Pediatric Dengue
Vaccine Initiative,
Rockville, Maryland,
USA*

of dengue diseases,” write Scott Halstead and colleagues, in a commentary that accompanies the study.

Moreover, cases that aren’t treated at hospital are rarely reported. The new data show that most of DALYs lost to the disease result from long illnesses that didn’t need hospital treatment. This suggests that previous estimates of the disease were overly conservative, according to Anderson and colleagues. “Inclusion of non-hospitalised cases is critical to accurately assess the total burden of dengue illness,” they say.

The inclusion of both mild and severe cases of the disease is one of the major strengths of the study, according to Halstead and colleagues. The work not only identified non-hospitalised cases, but also defined which cases were dengue fever and which were dengue haemorrhagic fever — a potentially fatal complication of the illness. This allows calculation of ‘expansion factors’ so that the disease burden for the whole Thai population can be estimated from the number of reported, hospitalised cases. For instance, the actual number of dengue cases was about four times the number of hospitalised cases in the study.

Similar studies should be carried out in different areas say Halstead and colleagues, to account for local variations in how the illness occurs, as its severity can be altered by nutrition, ethnicity, age, the genotype of the virus, and so on. “Quantification of [disease] burdens is crucial to the formulation by governments, donors, and industry of decisions for the prevention and management of dengue, especially for the potential introduction of dengue vaccines or other technologies,” they say.

Emergence of XDR-TB in Europe blamed on mismanagement

All sampled patients with extensively drug-resistant TB had received previous treatment for tuberculosis, a German and Italian survey reveals

As they report in this month’s issue of *Emerging Infectious Diseases*, Giovanni Battista Migliori and colleagues compared mortality rates and treatment outcomes in cases of multidrug-resistant (MDR) and extensively drug resistant (XDR) tuberculosis diagnosed by the TB clinical reference centres in Italy and Germany between 2003 and 2006.

Tuberculosis is usually treated by a number of ‘first-line’ antibiotics, but resistance to these drugs is a growing problem throughout the world. Tuberculosis that is resistant to both of the first-line drugs rifampin and isoniazid is defined as ‘multidrug-resistant’. According to WHO estimates MDR-TB is present in almost every country, and there are 450,000 new cases each year.

“Our findings suggest that mismanagement of TB cases plays a major role in emergence of the problem in Europe.”

Giovanni Battista Migliori, Salvatore Maugeri Foundation, Tradate, Italy

When the first-line treatments fail, doctors must fall back on a range of second-line medications that are more expensive and tend to have worse side effects. But even some of these are beginning to be circumvented by XDR-TB, which is very difficult to treat. To be classed as XDR-TB, the bacteria must be resistant to rifampin and isoniazid, to any fluoroquinolone and to one of the injectable second-line antibiotics capreomycin, kanamycin, and/or amikacin. XDR-TB cases have been reported in 23 countries, including all of the G8 nations.

Of the nearly 3000 TB cases analysed by the team, 4.4% were MDR and 0.4% (11 cases) were XDR. Worryingly, even in this small sample of XDR cases, more than two-thirds were resistant to all first-line anti-TB drugs, and two samples were resistant to all 12 antibiotics tested.

The XDR patients were five times more likely to die from the disease than the MDR patients, and those that survived needed longer hospitalisation and longer treatments. Moreover, all of the XDR patients and nearly 60% of the MDR cases (74 of 126 cases) had received previous treatment for tuberculosis. This indicates that the initial treatment did not kill off the disease and allowed drug-resistance to develop.

“Our findings suggest that mismanagement of TB cases plays a major role in emergence of the problem in Europe,” conclude Migliori and colleagues. “New rapid diagnostic tests and new drugs are urgently needed,” they say.

Safety trial of bird-flu vaccine positive

Inactivated-virus vaccine elicits immune response at lower dose, faster, and with fewer side effects than previous ones

“We report an inactivated whole virus vaccine that is safe and immunogenic in healthy adults and that requires a low dose and only one injection to trigger an immune response,” write Zoltan Vajo and colleagues in *Emerging Infectious Diseases*.

The Hungarian group developed the vaccine against the H5N1 flu subtype using the same procedure as for ‘FluvalAB’, an inter-pandemic flu vaccine that has been used in the country for the past 11 years. They tested its safety and immunogenicity on 146 healthy adult volunteers (65 men and 81 women), which is more than the usual 50 patients per group required to test yearly flu jabs in the European Union.

Three weeks after a single dose of the vaccine (6µg of haemagglutinin), both the test groups met the standards of immunogenicity set by the European Agency for the Evaluation for Medical Products (EMA). About 16% of the volunteers complained of

local pain around the injection site, but that faded after a day, and no other adverse responses occurred.

This single-dose regimen elicits an immune response more quickly than the vaccine recently approved by the US Federal Drug Administration, which needs two separate jabs of 90µg for best effect. “Using one, instead of two, injections will shorten the time needed to develop an immune response by three to four weeks,” point out Vajo and colleagues.

However, comparisons between the two vaccine trials cannot be made because of differences in the product, methodology, and study design, according to the US National Institute of Allergy and Infectious Diseases (NIAID). Inter-laboratory variability of antibody assays is substantial, partly because there are no international reference materials to standardise the assay systems. Moreover, NIAID cautions that how a vaccine would perform in the way of protection from infection or illness in a clinical setting cannot be predicted based on the immune response data alone.

One of the major differences between the two vaccines is that the Hungarian one uses aluminium phosphate as an ‘adjuvant’, to boost any immune response. Adjuvants are one of several strategies currently being considered by various authorities and manufacturers to try to stretch the limited flu vaccine supply.

“Adjuvants are not currently included as a component of US licensed influenza vaccines,” according to a NIAID statement. “Adding components to a vaccine adds another level of complexity to the manufacturing process and to clinical evaluation of the vaccine.”

The NIAID are currently trialling a DNA vaccine against H5N1 flu. “Together with its safety profile and desirable storage characteristics, [the DNA vaccine] would be a useful vaccine if it is efficacious, but the clinical trials need to be done,” they say. Production of such vaccines does away with the need to deal with the virus itself (even if it is inactivated), and it is a lot faster and more easily scaled up than other methods. The other advantage of DNA is that new prototypes can be generated more rapidly to keep up with viral variation. The trial started in January and is due to run for about a year.

“The most exciting step forward in years in this field.”

Fotis Kafatos, Chair of Insect Immunology and Genomics, Imperial College London, UK

The trick to taking over

Some cunning genetics enables GM insects to spread throughout a population, reviving hopes for using such organisms to control malaria and dengue fever

Chun-Hong Chen and colleagues have devised a ploy to propagate genetically modified insects in a population, they report in *Science*. The work is, “the most exciting step forward in years in this field,” says Fotis Kafatos, an insect geneticist at Imperial College London.

Mosquitoes that are poor at transmitting the malaria and dengue pathogens have long been hailed as a potential means to fight the spread of these diseases. Although such ‘refractory’ insects have been found in the wild and engineered in the lab, how to deploy them in sufficient numbers to make a difference is a major hurdle for this strategy; the refractory strain would have to make up a large proportion of the mosquito population to affect disease transmission.

Unless the refractory insects were to be released in vast numbers, they would need to have some selective advantage so that they could out-compete native strains to usurp the wild population through reproduction. Although a recent study found that a mosquito strain that is refractory to rodent malaria does seem to have a minor advantage over its wild-type peers when fed malaria-infected blood in the lab, this effect is probably not enough for them to take over in the wild.

So, refractory insects need to gain some active means to ‘drive’ their spread through a population. Now Chen, of the California Institute of Technology, and colleagues have engineered such an advantage: a ‘selfish’ DNA element that kills off insect embryos that don’t carry it.

They were inspired by a natural selfish gene called *Medea* that occurs in the flour beetle *Tribolium castaneum*. If a female beetle carries even one of the *Medea* elements, then so too will all of her live offspring; any embryos she conceives that don’t have it die. So the *Medea* gene spreads rapidly through populations.

Working in fruitflies, Chen and colleagues designed a similar selfish element based on a protein called MyD88, which is vital for embryonic development. Their artificial *Medea* element contains a gene that blocks any natural MyD88 expression during the development of the fly eggs. But it also has a ‘rescue’ gene that is switched on after fertilisation to supplement the embryos with extra MyD88 so they can survive.

The timing of the MyD88 block during egg development is such that all eggs in a female carrying a *Medea* element will lack MyD88 and be primed to die after fertilisation. The rescue gene will be switched on after fertilisation, but only in the embryos that inherit the element from the mother or father. In particular, if the mother carries only one copy of the element (rather than two), half of her eggs will not gain the element from her, and these will die after fertilisation if they do not receive a copy of the element from the father.

Chen and colleagues found that the idea worked as planned: embryos without the element died, and those that inherited a copy survived. In caged mating experiments the *Medea* element spread through a population in just 10 generations (beginning with an equal number of male and female flies, and with half

“In conclusion: inspiring and valuable results, hard work ahead.”

Fotis Kafatos, Chair of Insect Immunology and Genomics, Imperial College London, UK

of the male flies carrying two copies of the element, and all the other flies lacking it).

The authors suggest that a selfish element strategy could be made to work in mosquitoes and that a gene that stops the insects from transmitting disease could be spliced in between the killer and rescue modules of the artificial element.

It's a big step from fruitflies to mosquitoes, agrees Kafatos, but the current limitations are more like speed bumps than road blocks, and he expects them to be resolved soon. For instance, his lab has already submitted a paper for publication that identifies a large number of genes used during egg development and early embryogenesis in *Anopheles gambiae*, the mosquito that spreads malaria. So identifying the genes for a *Medea* element that will work in this species should be fairly straightforward.

The level at which a selfish genetic element like *Medea* would be needed to be introduced into the environment is another unknown and will require extensive analysis, according to Kafatos. “In conclusion: inspiring and valuable results, hard work ahead,” he says.

Super-absorbent gels to mop up solvents

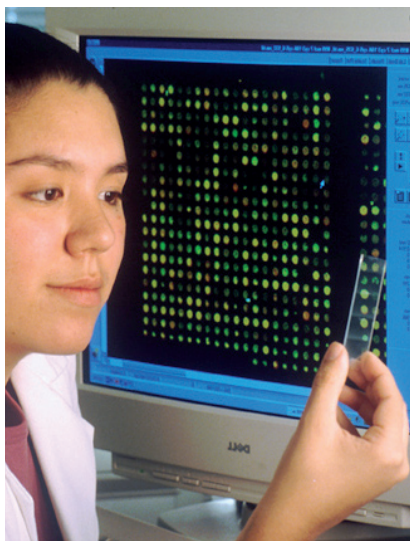
New materials could soak up industrial spills and oil, say chemists

Gels that expand by up to 500 times in a variety of solvents are revealed in *Nature Materials* by Toshikazu Ono and colleagues of the Kyushu University, Japan. “These materials could find applications as protective barriers for volatile organic compounds spilled in the environment and as absorbents for waste oil,” they predict.

The polymers are based on so-called polyelectrolyte gels which are already famed for their ability to swell up enormously in polar solvents such as water. These chemicals have found numerous uses from the linings in nappies to drug-delivery systems. However, there were no equivalent gels for non-polar organic solvents, such as dichloromethane and tetrahydrofuran, which are widely used in industry.

To design such materials, Ono and colleagues adapted the original polyelectrolyte gels by tacking on some bulky chemical groups that are more attractive to the non-polar solvents. The resulting gel absorbed large quantities of non-polar organic solvents such as chloroform and chlorobenzene, and even moderate amounts of highly non-polar chemicals like hexane.

Tweaking the make-up of the side-chains used will allow the performance of the gels in particular solvents to be optimised, the authors suggest.



DNA microarray technology.

(Source: NCI/Bill Branson)

Watching bugs clean up

Metal-reducing bacteria tracked during bioremediation using a microarray

The components and workings of microbial communities in the environment are often so complex that microbiologists give up trying to separate them out into the contributions of the individual species present. Instead, for simplicity, they prefer to treat the community as a whole, for instance sequencing an entire population in one go to find how all the genes function together in ecological processes such as carbon cycling.

Zhili He and colleagues wanted to monitor the dynamics of a bacterial community during a bioremediation study. Groundwater at the test site was heavily contaminated with uranium (up to 60 mg/l) but the microbial community reduced soluble uranium into an insoluble form. By day 670, the bugs had brought the soluble uranium down to the USA Environmental Protection Agency limit for drinking water (<30 µg/l).

To follow which bacterial processes were taking place and how they changed over this time, the team developed a microarray they term the GeoChip. The array can simultaneously monitor the expression levels of more than 10,000 genes from over 150 functional families involved in nitrogen, carbon, sulphur, and phosphorus cycling, metal reduction and resistance, and organic contaminant degradation. Their results suggest that *Geobacter*-type iron-reducing and sulphur-reducing bacteria had a significant role in purifying the ground water from uranium.

The authors propose that the microarray will be useful in studies of biogeochemical processes and the functional activities of various microbial communities important to human health, agriculture, energy, ecosystem management, and environmental clean-up and restoration. “[The GeoChip] is a powerful tool for tracking bioremediation processes, and for linking microbial populations to functional processes,” they say.

AVIAN FLU UPDATE

No more deaths

There have been no reports of further human infection or death from avian influenza A strain H5N1 in the past week.

Ghana has confirmed its first outbreak of the disease in poultry at a chicken farm east of the capital, Accra.

In Bangladesh, the virus has spread to six more poultry farms in the outbreak first detected on 22 March. The total number of farms infected is estimated at 38 with over 100,000 birds culled.

DISEASE OUTBREAKS UPDATE

West Nile starts early in the USA

Arizona’s first West Nile-positive mosquitoes of the year have been confirmed in Clarkdale in Yavapai County, health officials said.

“We’ve had some pretty heavy rains. That’s creating backyard breeding,” said Craig Levy, head of the state Department of Health

Service's vector-borne and zoonotic diseases section. "That's probably why we're noticing mosquitoes a little earlier than usual."

In 2006, the first West Nile-carrying mosquitoes were confirmed in late June in La Paz County. By October, the virus had infected 150 Arizonans and killed 11, health officials said. In 2005, there were 106 cases and four deaths, with 16 deaths and 391 cases in 2004, according to state statistics.

West Nile virus activity is beginning to show in the southern tier of states in the USA. Mississippi has already confirmed two human cases this year in figures correct to 12 April. Given the early start to the season, there may be more cases this year than last.

Malaria outbreak in India

The Assam Health Minister issued an alert on 1 May following an outbreak of malaria that has left 25 dead and affected nearly 10,000 others. "Between January and April, 25 people have died of malaria and 9721 people tested positive for the disease," Himanta Biswa Sarma said. "The disease has so far affected at least eight of Assam's 29 districts, with unofficial reports putting the death toll as high as 40. Doctors and paramedics have been put on alert across Assam with medical teams, including mobile units, fanning out to vulnerable areas to check the spread of malaria," he continued.

The situation is under control compared with 2006, when an estimated 304 people died from malaria in Assam. Northeastern India is a known 'malaria zone' with the disease claiming 500–600 people annually. While malaria can be fatal, it is a preventable disease. However, more than 1 million people die of malaria each year from the estimated 300–500 million cases.

Rift Valley fever outbreak continues to kill in Kenya and Tanzania

Nearly 700 cases of Rift Valley fever have been recorded in Kenya according to the Ministry of Health there. The outbreak has led to 155 deaths. In neighbouring Tanzania to where the disease spread, the number of regions affected has continued to rise with eight districts having reported cases. The total number of deaths in Tanzania now stands at 33, with 19 of those coming from the worst-affected Dodoma region.

The Tanzanian Red Cross has distributed mosquito nets, blankets, tents, and 4000 leaflets to educate the local communities about the disease.

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.