DISEASE WATCH | IN THE NEWS

A global problem

The largest survey of the global distribution of multidrug-resistant tuberculosis (MDR-TB) to date, which was based on data collected from ~90,000 patients with TB in 81 countries between 2002 and 2006, was published at the end of February by the WHO and International Union Against TB and Lung Disease. Based on the collated data, the WHO estimate that there are almost 9 million new cases of TB annually, 5% of which (500,000 cases) are MDR. In some countries, including Azerbaijan, Ukraine and Uzbekistan, the proportions of MDR-TB among new TB cases are higher, with the highest rate (22.3%) being found in Baku, the capital of Azerbaijan. This is the fourth global survey of TB resistance, but is the first to gather data on extensively drug-resistant TB (XDR-TB), which was detected in 45 countries. There was some good news: levels of MDR-TB in Estonia and Latvia, which had previously been identified as TB 'hot spots', have fallen substantially. **WHO**

Emerging patterns

A systematic, quantitative analysis of the patterns of infectious disease emergence over the past ~60 years was published in a recent issue of *Nature*. The authors began by going back through the literature from the period 1940–2004 and compiled a database of emerging infectious disease 'events', which they defined as the first time that a case or cluster of cases of a particular infection was reported in humans. They then analysed the variation in the frequency of these events over time and looked for any global temporal or spatial patterns of emergence. Over the 64-year period, 335 events, including the emergence of HIV and severe acute respiratory syndrome, were recorded. Perhaps unsurprisingly, zoonoses were the most common type of event, comprising 60.3% of all those recorded. The authors' analysis showed that 71.8% of these zoonoses originated in wildlife and that such events have increased significantly over the timescale examined. In terms of the practical implications of this interesting study, the group say that their data could form the basis for a predictive model to pinpoint hot spots for emerging infectious diseases. ***Nature***

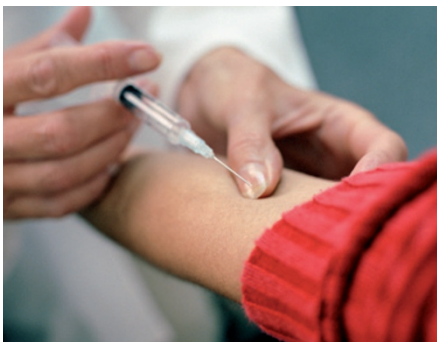
Inflammasome homes in on DNA

During bacterial and viral infections, the presence of pathogen-associated molecular patterns, such as viral RNA and bacterial and viral CpG-rich DNA, is detected by the innate immune system through a series of pattern-recognition receptors. Viral RNA is detected by endosomal Toll-like receptor 3 (TLR3), TLR7 and TLR9, as well as the cytoplasmic receptors RIG-I and MDA5, whereas viral and bacterial DNA is detected by endosomal TLR9 and the newly identified cytoplasmic receptor DAI. These receptors stimulate a type I interferon response. It was known, however, that viruses can also stimulate a TLR-independent pro-inflammatory response that involves tumour necrosis factor and interleukin-1β (IL-1β). A new report in *Nature* now reveals that the inflammasome is responsible for triggering this response through caspase 1. Tschopp *et al.* found that the response of human THP-1 cells to adenovirus DNA was dependent on NALP3 and ASC, two components of the inflammasome. This was confirmed as NALP3- and ASC-deficient mice showed reduced maturation of IL-1β in response to adenovirus DNA. Further experiments revealed that although NALP3 is the inflammasome component that is responsible for detecting viral DNA, the inflammasome can also detect bacterial DNA, cytoplasmic mammalian genomic DNA and synthetic DNA, and it is the ASC component of the inflammasome that is responsible for this more general function. ***Nature***

A fresh look at malaria

Approximately 2.3 billion people (35% of the world's population) are at risk of malaria, according to the first *Plasmodium falciparum* malaria risk map to be published in the past 40 years. Working under the auspices of the Malaria Atlas Project, a team of researchers combined national case-incidence data, health statistics and other sources of medical intelligence with information on factors that are likely to affect malaria transmission, such as climatic changes, and global population data to generate a map of the spatial distribution of the *P. falciparum* malaria risk in 2007. The map shows that ~1 billion people live in areas with a low risk of transmission, and the authors suggest that "an aggressive approach to *P. falciparum* elimination might be reconsidered as a more ambitious and achievable objective in many areas." ***PLoS Med.***

Boost for new vaccine research



Swiss-based pharmaceutical firm Novartis has become the first vaccine manufacturer to create a not-for-profit institute that is dedicated to developing vaccines for diseases that primarily affect developing countries. The new research institute — the Novartis Vaccines Institute for Global Health (NVGH) — is based in Siena, Italy, thus enabling researchers to benefit from the experience of the existing Novartis research centre there. Allan Saul has been recruited from the Malaria Vaccine Initiative at the US National Institute of Allergy and Infectious Disease to head the new institute. Initially, the NVGH will focus on agents of diarrhoeal infection, including *Salmonella enterica* serovar Typhi and non-typhoidal salmonellae, which are leading causes of morbidity and mortality in young children in developing countries. **Novartis**

Making strides with staph

Staphylococcus aureus researchers continue to make progress with two new papers published in *Science*. In the first study, Skaar and colleagues looked at the tissue abscesses that are caused by *S. aureus* infection. Such abscesses are typically infiltrated with neutrophils, but the specific neutrophil factor that is responsible for limiting *S. aureus* growth was unknown. Skaar and co-workers used imaging mass spectrometry in a mouse model of *S. aureus* infection to identify the host proteins present in the neutrophilic infiltrates and, combined with further analysis, they identified calprotectin as the host factor that restricts *S. aureus* growth. It does so by chelating Mn^{2+} and Zn^{2+}, and the authors therefore suggest that metal chelation could be a potential therapeutic strategy for *S. aureus* infections. In the second study, Oldfield and colleagues determined the crystal structure of *S. aureus* dehydrosqualene synthase (CrtM), a key enzyme in the biosynthesis of the *S. aureus* pigment staphyloxanthin, a known virulence factor. This structure was similar to that of human squalene synthase (SQS). The authors were intrigued by this finding, and they reasoned that inhibitors of SQS that have been developed as potential cholesterol-lowering drugs might also be active against *S. aureus* CrtM. Further analysis showed that *in vitro* some SQS inhibitors could also inhibit CrtM and caused attenuation of virulence in a mouse model of infection, thus providing proof of principle that cholesterol-busting drugs may be useful for tackling staph infections. ***Science***

Structural clues for Bunyaviridae

The Bunyaviridae family is a family of enveloped negative-strand RNA viruses that includes Rift Valley fever virus, Sin Nombre virus and Crimean-Congo haemorrhagic fever virus. Researchers have some knowledge of how bunyaviruses are packaged and infect cells, but because these viruses are pleomorphic detailed structural analyses have been lacking. A structural model for bunyaviruses is now available, as the three-dimensional structure of Uukuniemi virus (UUKV) has been determined by electron cryotomography. Some regular particles were observed, which enabled the authors to discern an unusual T = 12 arrangement for the glycoprotein spikes. Other enveloped viruses, such as flaviviruses, have a strict icosahedral structure. Interestingly, the authors found that the structure of UUKV virions is more flexible, and the authors propose that UUKV represents a 'borderline case' between strict icosahedral symmetry and pleomorphism. ***PNAS***

Mouse model for Chikungunya

Chikungunya virus first hit the headlines in 2005–2006, when a large outbreak of Chikungunya fever affected one-third of the population of Reunion Island and caused more than 200 deaths, even though fatalities had not previously been associated with the virus. Since then, more than 1 million cases have been reported in India, and the potential for global spread was illustrated by a substantial outbreak in Italy in 2007. Now, reporting in *PLoS Pathogens*, a collaborative group of French researchers report on the successful creation of a mouse model for Chikungunya fever. The authors found that neonatal C57BL/6 mice showed age-dependent susceptibility to Chikungunya virus infection, with mice less than 12-days old exhibiting severe disease. To investigate why adult mice are not susceptible to infection, the authors looked at the type I interferon pathway, which Chikungunya virus is known to trigger. Adult mice in which this pathway was partially or completely ablated developed mild or severe infection, respectively, indicating that type I interferon signalling is important in control of the disease. Detailed analysis of the progress of the infection in these disease models recapitulated features of the disease in humans, and fibroblasts were identified as the main cell type that was targeted by the virus. ***PLoS Pathog.***

Sweet specificity

The importance of the glycan specificity of influenza virus haemagglutinin (HA) in the human adaptation of avian viruses is often reported: the HA from avian viruses preferentially recognizes α(2,3)-sialylated host cell receptors, whereas the HA from human viruses preferentially recognizes α(2,6)-sialylated receptors. As reported in last month's Disease Watch, however, the story might not be quite so simple. Chandrasekaran and colleagues demonstrated that the specific structural

topology and length of the glycan linkage is important, with avian viruses preferentially binding to short-chain glycans and human-adapted viruses binding to long-chain glycans. The same group now take this work a step further with a new report in *Proceedings of the National Academy of Sciences USA* in which they dissect the biochemical rationale for this binding preference. The authors used quantitative analysis of HA–glycan binding in the prototypic 1918 H1N1 pandemic virus A/South Carolina/1/1918 (SC18), which showed an α(2,6)-binding preference and is transmitted efficiently, and in a mutated version of SC18 that carries a single amino-acid mutation in HA and is transmitted inefficiently. Using their assay, the authors were able to correlate the change in transmission efficiency with quantitative differences in HA binding to long-chain glycans. The authors conclude that screening HA mutants in this manner could be used to predict which viruses have pandemic potential. ***PNAS***

Outbreak news

Yellow fever. Following an epizootic outbreak of yellow fever in 2007, a small human outbreak has now been reported in Brazil. As of 1 February 2008, the Brazilian Ministry of Health had reported 48 cases, including 13 deaths. The Ministry had already made a request for additional doses of vaccine to the International Coordinating Group on Vaccine Provision for Yellow Fever Control to allow an emergency vaccination campaign to be undertaken. In neighbouring Paraguay, 16 cases have been confirmed, including 3 deaths, and emergency vaccination is also underway. **WHO**

In the News was compiled with the assistance of David Ojcius, University of California, Merced, USA. David's links to infectious disease news stories can be accessed on Connotea (http://www.connotea.org), under the username ojcius.