

SPECIAL REPORT

Dengue fever climbs the social ladder

Dengue fever was once a disease restricted to poor people in tropical areas. Its resurgence now threatens middle-class urbanites in cities such as Singapore. **Ewen Callaway** asks whether Asia's ever-growing wealth will propel a treatment or vaccine to market.

He was a 25-year-old rock-climber, educated to university level and from a middle-class family in Singapore. But last month, Ian Ng hit the headlines for the worst reason. He became the city-state's fourth and youngest victim of dengue fever this year. Ng was taken to hospital vomiting and feverish on 21 July, but he died from the mosquito-borne virus less than 24 hours later.

The booming cities of southeast Asia are experiencing their worst dengue outbreak in a decade — early rains and unchecked urbanization have promoted the spread of the virus-carrying mosquitoes. Singapore, which almost managed to wipe out the pandemic disease in the 1980s, has already had 5,000 infections this year. In Indonesia, more than 100,000 people have contracted dengue and 1,100 have died, coming close to the figures for all of 2006, according to the World Health Organization (WHO). Malaysia, Cambodia, the Philippines, Myanmar and Thailand are all experiencing a similar surge in the disease. Monsoon flooding across India, Nepal and Bangladesh threatens to worsen the situation by causing an explosion in mosquito populations.

Dengue infects at least 50 million people a year in more than 100 countries, mainly across Asia, Africa and South America. But unlike many diseases ravaging the developing world, dengue cuts across class.

"This is not a disease of the poverty-stricken, rural farmer," agrees Scott Halstead, scientific

director of the Seoul-based Pediatric Dengue Vaccine Initiative (PDVI), a non-profit organization launched in 2003 to drive a vaccine to market. In some developing countries, "the richer you are, the more likely you are to get dengue", he adds. This could be a reason for hope.

Dengue still plagues the poor people in urban areas, who face the brunt of a disease with neither cure nor vaccine. But as Asian economies boom, dengue is starting to interest pharmaceutical companies. "It's been enormously helpful to the field to see the potential market value of a dengue vaccine increase, and that has everything to do with rising incomes in Latin America and Asia," says Bruce Innis, who heads vaccine development at GlaxoSmithKline (GSK). "The reason why GSK and Sanofi-Aventis are in this business is shrewd business judgement," says Halstead.

Andrew Farlow, an economist at the University of Oxford, UK, who is working to determine the potential market for a dengue vaccine, says that there would be a substantial private market for a dengue vaccine in Asia and the Pacific. And the high economic toll that dengue takes in southeast Asia — US\$2.36 billion in the next 10 years according to the World Bank — means that middle- and high-income countries will be willing to pay more.

Spread by the bite of the female *Aedes aegypti* mosquito, dengue is caused by four *Flavivirus* strains. Those infected develop high fever and debilitating joint pain that can leave them bedrid-



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den for weeks. Infection with one strain provides lifetime immunity against that strain, but not against the other three. In fact, immunity from one strain boosts the chances of having a much more severe illness, called dengue haemorrhagic fever (DHF), because antibodies against another strain latch onto the virus and speed its entry into host cells. The result is immune overload, as blood vessels leak and the body goes into shock.

Target the hosts

Dengue fever isn't deadly, but DHF kills one in five if patients are not given adequate hospital support. More than 500,000 people — mostly children and infants — contract this more severe form of dengue, which kills 20,000 every year, making it a leading cause of childhood death in many countries. And the numbers are increasing.

Without an effective drug or vaccine, the only way to stem dengue is to go after its host. The mosquitoes flourish in small pools of clean water outside homes — tyres and plastic containers are some of their favourite spots.

Research frontline

In 2003, the Swiss drug firm Novartis launched its Institute for Tropical Diseases (NITD), a public-private partnership based in Singapore with a US\$7 million annual budget to produce drugs to combat dengue.

Several chemicals targeting key viral machinery have shown promise in the lab and NITD hopes to have an antiviral drug ready for

testing by 2009.

In the meantime, NITD is developing tools to quickly distinguish patients with dengue haemorrhagic fever (DHF) from those with dengue fever. For instance, patients with few white blood cells and platelets seem more likely to suffer from DHF.

GlaxoSmithKline (GSK), which is teaming up with the Walter

Reed Army Institute of Research in Washington DC, and Sanofi-Aventis have both launched expanded clinical trials of vaccines in Asia and Latin America, with results expected by 2009. Trials with tens of thousands of participants would follow.

GSK's vaccine is a mixture of four live viruses that have been weakened in a process called

attenuation. The viruses should provoke a lasting immune response, but not cause disease (R. Edelman *et al. Am. J. Trop. Med. Hyg.* **69**, 48–60; 2003).

Sanofi-Aventis has taken a different approach, genetically engineering a chimeric virus that contains molecular bits from each strain of dengue. (F. Guirakhoo *et al. Vaccine* **19**, 3179–3188; 2006). **E.C.**



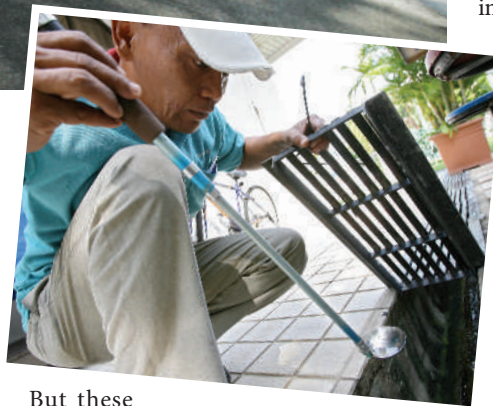
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Fever pitch: citizens of Singapore are urged to help prevent the spread of dengue fever. Officials are checking homes for signs of mosquitoes breeding.

Dengue is an almost exclusively urban disease — the WHO describes it as a “man-made problem related to human behaviour”.

“If they breed, you will bleed,” warns a pamphlet being distributed by the Singapore government that features a menacing mosquito. Unlike other countries in southeast Asia, Singapore has spent millions on mosquito control and surveillance, keeping a daily map of dengue hot spots. Citizens are fined up to S\$200 (US\$132) if mosquitoes are found on their property.



But these measures haven't stemmed the virus's spread in recent years, largely because of ineffective programmes in other countries, says Duane Gubler, a dengue expert at the University

of Hawaii in Honolulu. An influx of workers from neighbouring countries in which the disease is endemic transmits the virus to small pockets of mosquitoes in Singapore, Gubler says. Worse, decades of low infection rates have left the country's population with little immunity and now fewer mosquitoes are needed to spark an outbreak.

Until recently, there has been scant financial support for research and development of vaccines and treatments. But coinciding with an economic boom in affected cities, drug companies have begun pumping in money and manpower (see ‘Research frontline’). Dengue's immediate potential public and private market is unprecedented, says Harold Margolis, director of PDVI. In 2003, his firm received a \$55 million grant from the Bill and Melinda Gates Foundation, Seattle, Washington, to support development and testing of dengue vaccines, including gauging the costs and impact of a vaccine. And many in the field say an economic incentive improves the outlook

for a vaccine or treatment. “I'd rather be working with a company that feels positive they're going to get some reward,” Halstead says.

A dengue vaccine could have a market in the hundreds of millions, says Margolis, who is working to ensure that the vaccine will be available to everyone who needs it — not just those who can pay for it. A two-tiered market — public and private — is likely to emerge, catering to governments on one hand and to travellers, the military and foreign-aid organizations on the other, says Margolis. “You can sell it to the private sector, but it may not make dengue go away,” warns Margolis. “If that happens, that could severely affect the success of dengue vaccination.”

But a dengue vaccine is not a *fait accompli*, and a number of challenges could slow or derail development. One of the most important is the vaccine's safety. A successful vaccine would need to provide immunity to all four strains of the virus. Inadequate protection against any one strain could boost chances of coming down with DHF. And with hundreds of millions of people vaccinated, any slight safety problem will be magnified, says Halstead.

Although no one questions the need for a dengue vaccine, some wonder how far away it actually is. “We've been waiting for a vaccine for a very long time,” says Michael Nathan, dengue specialist at the WHO. He emphasizes the importance of continued mosquito control, which can address not just dengue, but other mosquito-borne diseases, such as yellow fever and malaria (see ‘Mosquito-borne diseases’).

In the meantime, Singapore and its increasingly wealthy neighbours may have to contend with more of Ng's generation falling to this indiscriminate killer.

MOSQUITO-BORNE DISEASES

Disease	Causative agent	Genus of mosquito	Estimated annual cases	Estimated annual deaths	Estimated countries affected	Vaccine status
Dengue fever	Dengue virus	<i>Aedes</i>	50-100 million	20,000	>100	In clinical trials
Yellow fever	Yellow fever virus	<i>Aedes</i> and <i>Haemagogus</i>	200,000	30,000	>42	Available
Japanese encephalitis	Japanese encephalitis virus	<i>Culex</i>	50,000	>10,000	>10	Available
West Nile fever	West Nile virus	<i>Culex</i>	Varies from year to year, depending on outbreaks	Varies	Africa, Australia, Europe, Middle East, Asia and North America	In clinical trials
Malaria	<i>Plasmodium falciparum</i> , <i>P. vivax</i> , <i>P. malaria</i> and <i>P. ovale</i>	<i>Anopheles</i>	500 million	>1 million	>105	In clinical trials

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