

Defeating dengue: a difficult task ahead

Dengue has reemerged in Latin America, but in Venezuela it never really went away. The health ministry has launched a new prevention campaign, but will it be enough?

As the developing world's cities and mega-cities grow, the female *Aedes aegypti* mosquito that spreads dengue among humans has become part of the urban landscape. Found in tropical and sub-tropical climates, the dengue vector lays its eggs anywhere clean water accumulates, including uncovered water storage drums, used car tyres, and discarded food and drink containers.

In July and August this year, the World Health Organization (WHO) Regional Offices for the Western Pacific (WPRO) and South-East Asia (SEARO) issued alerts about the increase in dengue cases. Indonesia reported that dengue cases doubled this year compared with the same period in 2005.

In Latin America, only Brazil had more total dengue cases in 2004 and 2005 than Venezuela, but the latter had a higher incidence per 100 000 inhabitants. Small countries like Costa Rica and Honduras as well as the small French overseas department of French Guiana had the highest rates of dengue.

After its 2001 dengue epidemic, which counted 83 180 cases, Venezuela had 30 693 cases in 2004 and 42 198 in 2005. Venezuela's health ministry reported 28 119 dengue cases in the period up to 21 July this year, up 15% from the same period last year and on track to continue the upward curve.

A campaign, led by the Pan American Health Organization, WHO's regional office for the Americas, helped to eradicate *Aedes aegypti* (also the urban vector of yellow fever) from most of South and Central America and some islands of the Caribbean by the early 1970s. These gains were not sustained, however, and the mosquito subsequently reinfested most of the region. This led to increasing transmission of

the dengue virus and, in 1981, the first epidemic of dengue haemorrhagic fever (DHF) in the region occurred in Cuba with 24 000 reported cases and 158 deaths. DHF produces internal bleeding and circulatory failure, and can be fatal. Venezuela had the region's second major DHF epidemic in 1990, amounting to 3108 reported DHF cases and 78 deaths.

Experts say that dengue's re-emergence in the region, is closely linked to the widespread presence of the mosquito vector and the circulation of all four of the distinct, but closely related, viruses

or serotypes (groups of closely related microorganisms). In 1970, when Latin America lived largely dengue-free, the region only had the DEN-2 serotype. Then DEN-1 entered the scene in 1977, followed by DEN-4 and a new strain of DEN-2 in 1981, this last virus

triggering the Cuban epidemic. DEN-3 was the most recent virus to reappear, after many years absence.

While infection by one dengue virus provides lifelong immunity to that serotype, it increases the risk of severe illness when an individual is later infected by any of the other dengue serotypes. As a result, hyperendemicity – the circulation of multiple serotypes – produces more DHF cases and more deaths.

Rampant urbanization and contemporary lifestyles have contributed to dengue's spread. "We have a much more consumer-oriented society with discardables, which when filled with rainwater breed *Aedes aegypti*," said Dr Michael Nathan, a dengue expert at the WHO's Geneva headquarters.

While heavy rains help create breeding grounds for the dengue vector by filling tyres and other discarded containers with water, scant rain also serves the mosquito well by forcing slum dwellers to store more water. Water drums without mosquito-proof lids are the perfect breeding ground for the *Aedes aegypti*. A regular supply of

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Dengue is transmitted by the bite of various day-feeding mosquitoes. Without a bednet, this girl inside the crib is exposed.

Irene Bosch/Anthony Guimaraes

drinking water would limit the need to store water around the household and thereby reduce vector density.

International trade and travel have accelerated dengue's recovery and spread, adds Nathan, "offering fantastic possibilities for the movement of the virus by infected travellers and of mosquito populations into new areas or back to areas where they had been eliminated". That explains how dengue was introduced on remote Easter Island where now it threatens to establish itself.

"In Venezuela people spend a lot of time outside," said Dr Renato Gusmao, the WHO Representative in Venezuela, "or inside but without protection. The easy access to blood increases the vector population." Public health experts recommend the permanent screening of buildings or the temporary use of air-conditioning in homes to reduce contact with the day-biting mosquito.

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A dengue vaccine still seems far off. For one, dengue remains a neglected disease for which there isn't much research funding, said Dr Irene Bosch, a Venezuelan researcher at the University of Massachusetts Medical School. Instead of seeing a vaccine as a panacea, however, argues Bosch, vector control and dengue prevention have to continue in parallel.

Recently, Venezuela's health ministry held a public event promoting its dengue and malaria prevention plan. For the plan's first stage, the ministry will invest US\$ 13 million, including the purchase of 128 vehicles, 550 fumigation tanks and 24 000 gallons (90 000 litres) of insecticide. Minister Jesus Mantilla said the plan was novel for Venezuela as it had been developed jointly with the communities. "As the community gets educated and changes their water, the vector will reproduce itself less," said Mantilla.



Irene Bosch/Anthony Guimaraes

The principal vector of dengue fever is the female *Aedes aegypti* mosquito. Once infected, a mosquito remains infective for life.

The government's public health policies are often blamed for the high incidence of dengue in Venezuela.

"Public policies are circumstantial and improvised," said Dr Julio Castro, a researcher at the Central University of Venezuela's Institute for Tropical Medicine. "I don't see any public policies regarding dengue. What are the logistics of dengue control for the next two years?"

The health minister promised there would be results within a month of launching the dengue and malaria prevention plan, and a substantial reduction in the two diseases within two to three years. ■

José Orozco, Caracas

South African study highlights importance of research involving children

More clinical trials involving children are needed to improve access to essential medicines. However, such trials pose ethical, scientific and practical challenges for researchers.

When 24-year-old Zama heard that her one-month-old baby girl had tested HIV positive, she did not believe it.

"To be honest, I found it difficult to accept that my baby and myself were HIV positive. I'm fit and my baby was not sick," she said, explaining her initial hesitation at joining a clinical trial for early antiretroviral (ARV) treatment of infants with HIV.

But Zama quickly accepted that both she and her baby were HIV positive, told her boyfriend and her sister, and enrolled her baby in the study.

One year later, Zama is one of seven mothers, feeding and playing with their healthy children in a bright room at Chris Hani Baragwanath Hospital. Mothers there told the *Bulletin* that they were glad to be part of the clinical trial.

Initial results from the Children with HIV Early Antiretroviral Therapy (CHER) study found a significant increase in survival among infants who received immediate ARV treatment. The trial started in July 2005 and is designed to continue through 2011. But a routine review by the trial's data and safety monitoring board in June this year, found that of the 377 babies enrolled, 96% were alive in the early treatment group compared to 84% in the delayed

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Zama, an HIV-positive mother from Soweto.

treatment group. The results were so striking that the board recommended that no additional infants be placed in the delayed treatment group and all babies be evaluated for initiation of ARV treatment.

The trial, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), highlights the importance of diagnosing HIV infected children within the first six weeks of life and facilitating early access to ARV treatment.

Zama said: "I did it for the sake of my child after she tested [HIV] positive. I gave informed consent when she was six weeks old. She has had no complications on treatment and is doing fine."

Another mother from Soweto, 26-year-old Ntebo, said it was



Claire Keeton

HIV-positive mothers, with nursing sister Valerie Kemesse, hold up their babies and toddlers, who have been participants in a groundbreaking antiretroviral treatment trial for infants.

difficult to disclose her HIV status to loved ones, however, it was necessary in order to treat her baby with anti-retrovirals every day.

She said: “The support we get here has made life easier. I trust the doctors and nurses, and my baby has had no sickness.”

Dr Avy Violari, lead investigator of the Soweto arm of the treatment trial, said disclosure of their HIV-positive status to partners and family was the main challenge for many mothers joining the study.

“You can’t hide the big bottles of syrup for treatment, which has to be taken twice a day,” said Violari of the University of Witwatersrand’s Perinatal HIV Research Unit. “Some mothers were scared to take them home ... [but] these babies were way too young to swallow a pill.”

Getting true informed consent can be another obstacle. All the mothers recruited in the trial took part in group screening sessions and individual sessions to help them understand what joining the trial would mean.

“They were also given a summary of the treatment to take home and when they came back they had another individual session with the doctor,” said Violari. “We would use diagrams and ask them questions to see if they understood. They also had a long informed consent form to sign. The forms were in seven different languages.”

The success of this trial – both its high participation and positive results – shows the huge potential benefits of doing clinical trials to develop and test medicines on children, despite the risks and challenges involved.

The World Health Organization (WHO) recently finalized the first list of essential medicines for children, which will be released in November. Dr Sue Hill, WHO’s technical expert on the list,

said the limited availability of appropriate children’s medicines contributes to childhood mortality.

The development of medicines for children lags years behind that of adults. Pharmaceutical companies, whose research agenda is mostly driven by commercial imperatives, do not always see a sufficient market to be gained among children.

The number of clinical trials among children has gone up in the United States of America where such trials are required by law, said Hill.

Davina Ghersi from WHO’s Clinical Trials Initiative said

her office is working towards a global standard register for clinical trials and would like to see more transparency in trials worldwide.

“Participation in a trial should not just be for the greater good of the community – it should be for the good of the individual too. It should not carry greater than minimal risk for the children either.”

Dr Avy Violari of the University of Witwatersrand’s Perinatal HIV Research Unit.

She said the two core issues in trials involving children are: Who is asking the questions and driving the research agenda? And, are the answers relevant to the public health needs in the countries doing the trials?

Hill said that more research into children's medicines is needed. One

focus is developing different dosage forms besides liquids, which are bulky, heavy to transport and tend to have a shorter shelf-life than tablets. She said some medicines tasted unpleasant and were difficult for children to swallow, for example the ARV drug ritonavir.

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Claire Keeton, *Soweto*

Saving mother's lives in rural Indonesia

Indonesia's maternal mortality rate is one of the highest in south-east Asia. One East Java district has introduced a novel scheme to reduce those deaths.

In many rural areas of Indonesia, traditional ways of delivering babies remain popular. For example, in Ugaikagopa in the country's east, traditional healers take the pregnant woman to the middle of the forest to deliver the baby. They may use fibres taken from bamboo to cut the umbilical cord and wipe the newborns' bodies with guava leaves.

The instruments used are not sterile and can lead to infection. The traditional healer, or *dukun* in Indonesian language or Bahasa, may not be able to deal with complications during labour, and by the time the mother gets to a local clinic it may be too late.

As a result, maternal mortality in Indonesia is high compared to most south-east Asian countries. In 2005, there were an estimated 262 maternal deaths per 100 000 live births, compared with 39 per 100 000 in Malaysia and 6 per 100 000 in Singapore. Figures for Papua province from 2003 show even higher death rates: 396 per 100 000 live births.

The chief cause of maternal death in Indonesia is bleeding, followed by eclampsia, infection, and the complications of abortion and prolonged labour. Most of these deaths occur with births handled by traditional birth attendants rather than by medically trained health-care professionals.

Many families prefer to use a *dukun* because of traditional beliefs and because it is a cheaper option than

using a trained midwife or going to hospital. In addition, these traditional birth attendants do household chores while mothers recover.

A scheme in Ngawi district in East Java has been initiated to try to ensure that a midwife or other trained birth attendant assists deliveries. Since 2006, *dukun* are given incentives of up to IDR 100 000 (US\$ 12) for referring pregnant women to skilled birth attendants or community-based midwives. Funding comes from the local government budget.

Mbah Dinah, 60, a traditional healer in Ngawi, said, "We escort the pregnant woman to the community

health centre during daylight. At night, we escort them to the midwife's house."

Additionally, the *dukun* receive a small sum of money when they assist a midwife. They are responsible for taking care of the cord and for bathing the newborn – supervised by the midwife – during the first week. The patient makes the payment; the amount depends on the length and type of services provided.

This way, *dukun* do not feel threatened by the arrival of a skilled birth attendant or community-based midwife in their area, but are happy to cooperate.

Sumarikh, 24, is from the village of Majaseem and was nine months pregnant. She said she preferred to be examined and give birth aided by a midwife because she feels it is safer: "Devices that are used are sterile and midwives know how to handle any complications fast." She was examined monthly in early pregnancy, and every week in the ninth month.

The scheme is proving successful. In 1984, a total of 86% of deliveries in Ngawi were aided by *dukun*, compared with fewer than 1% of deliveries today. Maternal deaths also have

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Mbah Dinah, traditional healer in Ngawi, East Java province.



A *dukun* in Ngawi, East Java escorts a pregnant woman to a midwife.

Cirinta Analen



WHO/Tala Dowlatshahi

Traditional healers in Ngawi, East Java.

decreased: while 15 mothers died during delivery in 2002, this number dropped to 9 in 2006.

Awareness of the risks of delaying transfer of pregnant women to health centres also has grown as a result of the Program Gerakan Sayang Ibu (To Love Mother Programme in Bahasa). This information programme prompted many villages to provide transportation to transfer pregnant women either to community health centres or midwife delivery huts.

These initiatives are part of WHO's Making Pregnancy

Safer strategy, which was launched in 1999 with support from the United

Nations Population Fund (UNFPA), the United Nations Children's Fund (UNICEF) and the World Bank. Making Pregnancy Safer in Indonesia has three key principles: every delivery should be attended by a skilled birth attendant, every complication should be referred and managed appropriately, and all reproductive-age females should have access to contraceptives and post-abortion care. The Indonesian government has set a

target to lower the maternal mortality rate to 125 per 100 000 live births by 2010.

The ministry of health initiated a midwifery education programme from 1989 to 1996 that trained more than 54 000 community-based midwives. Due to this programme, the proportion of deliveries assisted by a skilled attendant throughout Indonesia has risen from 25% in the early 1990s to 76% in 2006.

"We know what interventions are necessary in order to save pregnant women and newborns' lives," said Dr Monir Islam, Director of the Making Pregnancy Safer department at WHO. "The technical battle we have won; now the time has come to win the political battle for policy changes and increased investment." ■

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