

SARS virus returns to China as scientists race to find effective vaccine

SARS returned to China's Guangdong Province last month prompting a mass cull of wild animals suspected of contributing to the spread of the disease. However it is unlikely that vaccines being developed by scientists in Canada, China, the United States and other countries will be ready for an outbreak in 2004.

Chinese authorities and WHO officials said on 5 January that a 32-year-old Chinese television producer had tested positive for the SARS virus that infected about 8098 people and killed 774 people in 26 countries last year. People who had been in close or normal contact with him have not developed symptoms. It was the first confirmed case of SARS since last summer, apart from two research scientists in China (Province of Taiwan) and Singapore who became infected while conducting laboratory experiments in September and December.

A 20-year-old waitress who fell ill on 25 December was put in an isolation ward with a suspected case of SARS on 31 December. The woman, a migrant worker from Henan Province, worked in a restaurant in Guangzhou, the capital of Guangdong, the Chinese region where the virus is thought to have first surfaced in November 2002.

It was still unclear whether Chinese authorities have another "outbreak" on their hands or isolated cases. Under new WHO guidelines due to be issued in January, if one person infects another, this would constitute "an outbreak." However, no link has been established between the television producer and the waitress, according to WHO.

Scientists are investigating the TV producer and the waitress in the hope this will lead them to the source of the virus which could be in animals, humans or the environment. Following an investigation of the restaurant where the waitress worked, WHO said on 16 January that it had found strong evidence that civet cats — a gastronomic delicacy in China — are linked to the

disease. The restaurant is believed to have served wild animal meat including civet.

"I think there is very good evidence to think animals are the reservoir and the way the disease gets started," said WHO researcher, Dr Robert Breiman. The television producer, however, told Chinese media after being discharged from hospital on 8 January that he had never eaten civet cat.

More than 100 people who had been in contact with the television producer and the waitress were placed under quarantine or observation, but have not shown any symptoms.

A 35-year-old man was isolated on 6 January and identified by Chinese health authorities as a third suspected SARS case in Guangdong Province this year, but laboratory analysis has yet to confirm that his illness was SARS. The third new suspected case has fuelled fears of a new SARS outbreak.

An obstacle to tackling such an outbreak is the lack of early diagnosis. A polymerase or chain-reaction (PCR) test can only identify the virus 8 or 9 days after infection, by which time the



One of the enclosed beds designed to contain disease-infected travellers at the border checkpoint in Nanjing, China's eastern Jiangsu Province.

patient may already be infectious. In the absence of effective early diagnosis, the race to find a vaccine is on.

Dr Marie-Paule Kieny, Director of WHO's Initiative for Vaccine Research, said that although there were many projects under way to find a SARS vaccine, effective immunization would not be available for at least one and a half to two years.

Beijing Kexing Bio-product Company, a subsidiary of Chinese firm Sinovac Biotech Ltd, have announced that they will initiate phase one clinical trials in humans in January 2004, using a killed SARS vaccine which produced good results in monkeys. Kieny said that this project appears to be more advanced than a plethora of rival projects.

The University of Pittsburgh in the US State of Pennsylvania, is developing a genetically engineered vaccine that has gained a lot of attention. Kieny explained that it was based on a recombinant adenovirus. "They have had good results in monkeys, but as far as I know they will not be ready to start clinical trials before the second half of 2004," said Kieny.

Researchers on a project led by the Pasteur Centre in Hong Kong Special Administrative Region have also come up with a vaccine and are currently immunizing mice. Kieny explained that "this involves the preparation of candidate vaccines based on various forms of the spike glycoprotein purified from mammalian cells."

There are several other SARS vaccine projects using killed virus, like those being developed by big pharmaceuticals Chiron in the United States, Aventis Pasteur, the vaccines business of French pharmaceutical giant Aventis, and Baxter International Inc. In Switzerland, a measles-based attenuated viral vector is being investigated by Berna Biotech.

"It's impossible to say at this stage which of these vaccine candidates will succeed and make a real product," said Kieny. ■

Fiona Fleck, *Geneva*

Mali takes grass roots approach to ending female genital mutilation

The Government of Mali has taken action against the widespread practice of female genital mutilation. During a four-day meeting funded by UNICEF and

held in the capital city, Bamako, the government agreed to assist local activists and religious leaders engaged in grass-roots efforts to eradicate the custom by involving them in a national campaign.

"The meeting was an important milestone in our struggle against female genital mutilation," said Fatoumata Sire Diakite, President of the Mali branch of the Inter-African Committee on Traditional Practices Affecting the Health of Women and Children, an NGO with regional headquarters in Addis Abbaba, Ethiopia, and National Committees in 26 countries in Africa. "Government representatives listened to all of us, showed their concern and indicated their commitment to help us. This is a big change — a wonderful change — from the government's former stance, which was frankly hostile," said Diakite.

Mali is one of the countries with a very high prevalence of female genital mutilation: at least 95% of the West African country's female population have undergone the procedure that involves the partial or total removal of the external female genitalia or other injury to female genital organs — a custom that has formed part of social life for centuries. The procedure can lead to negative health consequences including infertility, reproductive tract infections, obstructed labour and increased susceptibility to HIV/AIDS, hepatitis and other blood-borne diseases.

Other countries with a high incidence of female genital mutilation are Guinea, Somalia and Egypt. In all, an estimated 100 to 140 million girls and women from 28 countries in Africa and the Middle East are estimated to have undergone some form of this harmful practice. No less than 26 million young women have been subjected to infibulation — a radical form of the procedure that involves stitching or narrowing of the vaginal opening. Around two million female children continue to be at risk each year.

Participants at the Bamako meeting reviewed progress and developed new, community-focused, strategies to curb female genital mutilation. The government agreed to incorporate training on how to combat the custom into the national training programmes for teachers and nurses and called for a national summit meeting at which the problem will be debated in public. In an attempt to reach Mali's 10 million Muslims — who represent approximately 90% of

the population — participants agreed to draft a brochure about female genital mutilation in Arabic and to disseminate it to Islamic religious institutions.

Despite mounting pressure from international organizations such as UNICEF and the European Parliament, Mali's government has been reluctant to prohibit female genital mutilation by law — a step Diakite says local activists see as vital. "We need a law against this practice, and we need it fast," she said.

Some international workers, however, argue that Mali is right to proceed cautiously. "Given that most people here are committed to the practice, the government is convinced an outright ban would not stop female genital mutilation but rather drive it underground," said Sarmoy Cisse, WHO Program Administrator for Family and Community Health in Mali.

In Mali, as in other societies where the practice is prevalent, it is woven into the local belief system, Cisse explained. "These are customs that date back a long time. Changing them is complex and requires sensitivity."

In many places, women themselves keep the practice alive, explained Dr Heli Bathija, WHO Area Manager for the African and Eastern Mediterranean Regions' Department of Reproductive Health and Research. "They see it often as a religious obligation or a condition for marriage," she said, adding that a ban alone is unlikely to be effective. Bathija advocates a shared commitment by NGOs and religious and community leaders to shift attitudes through education, with support from local government and international organizations.

Mali's new grass-roots strategy is similar to some approaches taken by countries who have been successful in reducing female genital mutilation. "We have seen positive results in many places, for instance in Kenya, Uganda and Egypt. In Senegal women have taught other women about human rights, health and sanitation, which prompted them to see female genital mutilation as unnecessary," Bathija said.

In Senegal, Tostan — an NGO funded in part by UNICEF — has been tackling the female genital mutilation problem village by village. The result: some 1271 communities — more than a fourth of Senegal's villages — committed to ending the practice since 1997.

Tostan also has initiated programmes in Mali, Guinea, Burkina Faso and Sudan.

According to Dr Djamila Khady Cabral, Regional Counsellor for the Family and Reproductive Health Division of the WHO Regional Office for Africa, laws can help further diminish the practice only when local people have already decided for themselves to stop the custom. "In Senegal and Burkina Faso, for example, recent laws prohibiting female genital mutilation have created a more favourable environment and made women feel they are protected," she said.

Preliminary results from a national survey launched by the government of Burkina Faso to establish whether a 12-year campaign against female genital mutilation has been successful, have indicated that the practice has been almost wiped out in some parts of the country.

Not all African governments, however, are following suit. A recent situational analysis of Female Genital Mutilation in the Gambia, commissioned by UN agencies including WHO and UNICEF, blamed government interference for recent setbacks in the local campaign against the practice. Although the government prohibits the custom, 80% of Gambia's female population are still prone to it. Lack of media access for anti-female genital mutilation activists was highlighted as a major obstacle to reducing this figure. ■

Judith Mandelbaum-Schmid, *Zürich*

Science meets tradition and identifies herbal treatment for jaundice

Researchers at the Baylor College of Medicine in Houston, Texas, have shed light on how a Chinese herbal tea used for centuries to treat neonatal jaundice works (*Journal of Clinical Investigation* 2004;113:23-5). The finding could lead to new drugs for the ailment in infants as well as adults.

Characterized by yellow-tinged skin and eyes, jaundice is the build-up of bilirubin, a yellow-red pigment formed and released into the bloodstream during the natural breakdown of red blood cells in the liver. According to the American Academy of Pediatrics, more than half of all infants in the US develop the condition during their first week of life, most often because they have immature livers and a surplus of red blood cells.

The condition is typically remedied by exposing a baby to sunshine for a few minutes a day or, in severe cases, lamps that emit specific wavelengths of light. In China, however, babies are given Yin Zhi Huang, a tea made from Yin Chin (*Artemisia capillaris*), a relative of wormwood, and three other herbs. "Interestingly," says David Moore, who led the current study, "wormwood is also used in Western traditional medicine for treating liver problems."

Moore and colleagues decided to explore Yin Zhi Huang as a follow-up to earlier work in which they showed that a protein found in liver cells, constitutive androstane receptor (CAR), was activated by bilirubin and regulated its removal. Knowing that wormwood tea also boosted bilirubin clearance, the researchers guessed that an active ingredient in the herbal brew might also "switch on" the protein.

Their hunch proved correct. Yin Zhi Huang and a tea steeped from Yin Chin alone speeded bilirubin removal in normal mice, but not in mice genetically engineered to lack CAR. Furthermore, the researchers found that 6,7-dimethylesculetin, a component of both Yin Zhi Huang and Yin Chin acts on CAR and accelerates bilirubin clearance.

The discovery that the compound activates CAR may lead to new drugs that prevent or treat jaundice by specifically targeting the receptor protein. However, such pharmaceuticals will not necessarily be based on 6,7-dimethylesculetin. "It's not the world's greatest CAR activator," says Moore.

Moore suspects that CAR and its relatives in the nuclear receptor superfamily are the targets of active agents in many natural products and herbal medicines, which are biologically active but whose mechanisms are unknown.

However, studies that look to herbal remedies for clues to modern pharmaceuticals are rare. "Despite the fact that years ago all medicines came from plants and natural products, there has been a dramatic change over the last 100 years in the way we discover new medicines," says Moore. "I'd say the dominant theme these days is definitely not searching natural products."

While herbal remedies provide a medley of compounds thought to restore a holistic "balance" to the body, Western pharmaceutical products are increasingly based on purified molecules

that act on specific biological targets. In addition, "purified compounds extracted from herbal remedies have a 90% failure rate in clinical trials," says Xiaorui Zhang, Coordinator of WHO's Traditional Medicine programme. "The synergistic effect between the different chemicals in a plant or plants has to be taken into consideration."

However, WHO actively encourages research on the traditional use of herbal medicines, especially those that alleviate symptoms of diseases, such as malaria and AIDS. It has also developed guidelines for the clinical testing of traditional therapies and sponsors several centres worldwide that are compiling a database, in English, of information on natural medicines.

None the less, with the annual global market for herbal remedies estimated to be around US\$ 23 billion and growing, many scientists think studies like those conducted at the Baylor laboratory help bridge the gap between traditional and Western-style medicine. "For mechanism-based scientists and physicians ... it is both satisfying and reassuring when a single component of a herbal remedy turns out to function via a defined mechanism," notes Mitchell Lazar of the University of Pennsylvania School of Medicine in a commentary that accompanied Moore's report. "This is a wonderful example of knowledge gained by applying the Western scientific method to an Eastern herbal remedy." ■

Charlene Crabb, *Paris*

Delays in legislation slow the progress of CME in India

Indian medical associations say their doctors desperately need continuing medical education (CME) to keep them up to date with the latest drugs, equipment and medical practices but legislation to make this a requirement has made little progress.

The Medical Council of India is campaigning for CME to be made compulsory, as it is in the UK and some US states, for the country's 615 000 registered doctors and has proposed a draft amendment to a law that would standardize medical practice across the country while making sure it is up to date with the latest developments.

If passed into law, mandatory CME for registered doctors in India could set a precedent for other developing countries but some Indian doctors say their medical

associations have failed to lobby hard enough for this and lawmakers have been slow to respond.

"There is resistance to change by [health] professionals who lack the opportunity for undergoing good quality CME, and lack incentives as well as motivation for attending CME programmes," said Dr P.T.

Jayawickramarajah, Coordinator at the WHO's Regional Office for South-East Asia in New Delhi.

Other doctors in India fear that without CME courses, lack of up-to-date knowledge can endanger lives and perpetuate out-moded practices. Umesh Kakrania of SPARSH, a support group for people with HIV/AIDS, said that many Indian doctors were still recommending single or double anti-retrovirals rather than triple combinations which are standard. "Several premature deaths have occurred due to this sad situation," Kakrania said.

Kakrania said that many doctors, paramedical and nursing staff in India still suffered from the "anti-AIDS phobia" of the past and urgently needed to improve their basic medical education. He said many medical staff still refuse to touch HIV positive patients.

Dr Shekhar Saxena, an Indian physician who works at WHO in Geneva, said that enacting a legislation to make CME mandatory is a necessary but not sufficient requirement for delivering quality knowledge and skills to practicing doctors in India.

"Allocation of substantial funds and professional resources will be needed to really make the system work and it is important that pharmaceutical companies are not allowed to dictate this agenda based on their financial power," said Saxena.

Despite the lack of legal incentive for doctors to attend regular refresher courses, CME has been catching on in India over the last three years partly due to the efforts of regional medical associations.

Dr Puneet Bedi, a gynaecologist in Delhi, however, believes that doctors' attitudes will change as more doctors in India realize they must keep up to date with the latest medical practice, but progress is slow. "We are moving extremely slowly in promoting CME," said Dr B.V. Adkoli of the All India Institute of Medical Sciences in New Delhi.

The Delhi Medical Council, which represents 24 000 doctors in the capital,

made it mandatory two years ago for members to complete 100 hours of CME every five years before they can re-register as doctors.

CME programmes have also been held in Belgaum, Mangalore, Madurai, Manipal and Tirunelveli in the south, Dharamshala, Aligarh and Muzaffarnagar in the north, Bhopal, Nagpur and Jaipur in the west and Cuttack, Patna and Guwahati in the east but doctors in many rural areas are still missing out as they have little or no access to such courses.

CME is a requirement for the registration of health professionals in many developed countries, such as the United States, but CME opportunities are limited in the developing world because of the lack of legal or other incentives, according to a study called Promoting Rational Use of Medicines published in September 2002 by WHO's Essential Drugs and Medicines Policy Department.

Last year, the Medical Council of India established a code of ethics stating that members should complete 30 hours of CME every five years in order to re-register as doctors, but only about 20% of India's doctors follow this as it is not legally binding.

Now the Medical Council of India wants the Indian parliament to enshrine this principal in law by amending the Indian Medical Council Act of 1956 that governs medical practice across the country. In September 2002, the Indian daily newspaper, *The Times of India*, reported that the proposal was "gathering dust."

"We want registration to be for a period of five to seven years with re-certification subject to CME attendance," Dr A.R.N. Setalvad, Secretary of the Medical Council of India, adding: "The proposal is still under consideration and nothing can be done until the act is amended by the parliament". It was unclear when the draft proposal would come up for review or be debated, and whether it had a chance of being passed into law.

Some doctors say that one solution to the impasse could be for more regional medical associations to take the lead, like the Delhi Medical Council, and make CME a requirement for re-registration of doctors and other health professionals. This, they hope, could have a knock-on effect across the country.

The response to requiring doctors in the Indian capital to undergo CME re-training has been positive. Dr S.K.

Khattri, Secretary of the Delhi Medical Council, said the Council had conducted 316 courses since the start of its CME programme in mid-2000.

CME courses in India are funded by a wide range of organizations: the Medical Council of India, which says it spends US\$ 330 000 on CME a year, international organizations such as UNICEF, private firms such as Indian generic drugs companies, as well as the Indian Ministry of Health.

Amit Sengupta of the Delhi Science Forum, a New Delhi-based body for scientific research and advocacy, said that because of low literacy levels and poor awareness of good medical practice at the community level, there is little pressure from patients to motivate doctors to participate in CME programmes, despite what he referred to as the "dismal quality" of the medical service.

"Most people see the medical professional as someone next to God, so there is very little questioning of norms or practice," Sengupta said. ■

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