

UK report urges screening for "mad sheep" disease

The United Kingdom's Food Standards Agency has called for urgent development of new ways of detecting whether mad cow disease, or bovine spongiform encephalopathy (BSE), has spread to sheep.

In a report on anti-BSE measures in the United Kingdom, the agency warns that current research is too slow and says that if BSE is found in the 40 million-strong national sheep flock, existing controls would have to be revised.

There has been growing concern that some of the 4000 sheep who die of scrapie each year in the UK may have been suffering from BSE, which was first identified as a neurological disease of cattle in 1986. In 1996, the UK's Spongiform Encephalopathy Advisory Committee reported that scientists had successfully infected sheep by feeding them with infected brain tissue.

"The current research to look for BSE in sheep is costly and slow," says the report. "As a matter of great urgency, there is a need to develop and apply a rapid screening method so that large numbers of sheep can be tested to reduce the uncertainty of whether or not BSE occurs." The report also urges a complete ban on intra-species recycling of blood, gelatine and tallow in animal feed, as well as checks on sheep intestines used for sausage casings to ensure that the processing removes lymphoid tissue. The possibility that some cattle and sheep may be carriers of BSE without developing the disease has also to be looked into. There are fears that if BSE is found, slaughtering of affected sheep flocks may have to be considered.

The move by the agency comes hot on the heels of publication of the report of an official enquiry into the BSE crisis in the UK. The report says that putting animal protein in cattle feed was "a recipe for disaster" and that the government at the time was preoccupied with preventing an alarmist over-reaction to BSE. The report of the enquiry, which took two years and cost almost £30 million (US\$ 42 700) to produce, said there were bureaucratic delays in responding to scientific warnings about the risks, but no deliberate intention to deceive.

Up to early November this year, variant Creutzfeld-Jakob disease (vCJD), the human form of BSE, has killed at least 80 people in the United Kingdom, 3 in France and 1 in

the Republic of Ireland. More cases are expected, especially in the United Kingdom, where the government has now agreed to compensate vCJD sufferers and their families.

In France, a nationwide scare over BSE was triggered in October by potentially infected meat finding its way onto the shelves of three supermarkets. In mid-November the government responded to public fears by mandating compulsory random testing of all herds and banning the use of meat and bone meal in animal feed. The government is now facing court action by the families of two victims of vCJD demanding compensation. Sales of meat in France have fallen by 40%.

In a further blow to French cattle farmers, on 17 November, Italy banned imports of French cattle more than 18 months old and of French beef on the bone. Similar bans of French meat imports have been announced by Austria, Brazil, Greece, Hungary, Poland, Portugal, Russia, Spain and Switzerland, according to press reports. The Italian government has also banned the use of meat and bone meal in animal feed for herbivorous animals and has plans to screen all cattle more than two years old for BSE. In doing so, it is complying with a 1994 European Union decision to prohibit the feeding of mammalian protein to ruminants throughout the Union. ■

Roger Dobson, *Abergavenny*

The Uganda Ebola outbreak— not all negative

The latest epidemic of Ebola haemorrhagic fever, that began on 8 October in the Gulu district of northern Uganda, had, as the *Bulletin* went to press, claimed 337 victims, with 121 deaths. By mid-November, the outbreak had essentially run its course and WHO epidemiologists considered it under control.

The speed with which this epidemic was snuffed out — in a matter of weeks instead of months — is one feature distinguishing it from most of the eight known previous epidemics. Those outbreaks occurred in Sudan in 1976 and 1979, Gabon in 1994 and 1996 (twice), Côte d'Ivoire in 1994 and Zaire (now the Democratic Republic of the Congo) in 1976 and 1995.

One reason for the rapid outcome, in the view of virologist-epidemiologist

Ray Arthur, WHO's focal point for viral haemorrhagic fevers, was the fact that Uganda very quickly brought WHO into the picture, rather than making a broad appeal for international assistance, as had been the case in previous epidemics. "As the coordinating body, we could rapidly muster the experts and equipment, and get the logistics going to handle the crisis," Dr Arthur says. WHO also launched an international appeal for funds, to the tune of US\$ 848 000, to cope with the outbreak. At this writing, WHO's partners have given US\$ 1.3 million. The team assembled by WHO included experts from the US Centers for Disease Control and Prevention (CDC), Médecins-sans-Frontières & Epicentre, the Italian Istituto Superiore di Sanità, the International Committee of the Red Cross (ICRC), Japan, Germany, and several other institutions. All are part of a global epidemic "alert-and-response" network.

A key logistic element that "really helped get us on top of things", according to Dr Arthur, was the setting up, for the first time, of a field lab at the site of the outbreak. The lab could test blood samples on the spot, allowing rapid diagnosis of suspected cases and enabling the team to follow close on the heels of the virus as it spread in the community." And spread it did, not so much from the hospital, Dr Arthur says, which was the main source of "amplification" in several previous epidemics, but rather from funerals. "The virus was very likely transmitted when people washed cadavers, or simply through close contact during the funeral."

The Ugandan epidemic, with about 40% of infected people dying, seems to have been less lethal than previous outbreaks: the case fatality rate in the Sudan outbreaks, with a virus of the same "Sudan" group of strains as in Uganda, was 50–70% and that of the Zaire outbreaks, with a "Zaire" strain, 70–90%. Dr Arthur believes the difference could be related to a more efficient surveillance system picking up cases more quickly and permitting earlier treatment. "The treatment itself may also have had something to do with it," he says. "We made a special effort to prevent these patients from dehydrating by giving them oral or intravenous fluid replacement."

Not all was plain sailing, though. The presence of civil disturbance in the Gulu area

hampered movement of the Ebola team, particularly at night. Some villagers, captured by rebels, can thank the Ebola outbreak for their freedom: the rebels quickly released them when they heard they were from the Gulu area.

Particularly tragic has been the fate of many of the victims of the outbreak who survived the infection. Despite educational messages about the infection and the precautions that survivors should take — avoiding unprotected sex for a few months, for example, since the virus can be found in sperm up to three months after clinical cure — many survivors on returning to their homes were spurned by fearful villagers and found their possessions and dwellings burned to the ground.

Among the unknowns of Ebola haemorrhagic fever is the reservoir of the virus in which it shelters between epidemics. An international team of virologists has for several years been in the Tai Forest, in Côte d'Ivoire, combing the jungle for anything that "moves, flies or crawls", as Dr Arthur puts it — so far to no avail.

Some progress, however, is being made in identifying what may be early warning signs of Ebola outbreaks. WHO and researchers from the US National Aeronautics and Space Administration (NASA), using satellite imaging and rainfall data, have noted a pattern suggesting a link between rainfall after unusually dry weather and the onset of an outbreak. They are currently studying whether the current Uganda outbreak fits this pattern. "I'd take a bet that this particular epidemic may be just the start of a new cycle of Ebola outbreaks," says Dr Arthur. "But I hope I'm wrong." ■

John Maurice, *Bulletin*

Malaria drug resistance gene identified

A US research group headed by Tom Wellems of the US National Institute for Allergy and Infectious Diseases (NIAID) announced at the end of October that they had identified a gene which mutates to make the most lethal of the malaria parasites, *Plasmodium falciparum*, resistant to chloroquine. The gene, dubbed *pfert*, is on chromosome 7, and codes for a protein on the surface of the parasite's stomach. The NIAID group identified the *pfert* gene by crossing chloroquine-sensitive and chloroquine-resistant species of the parasite

and by using molecular biology techniques to locate the gene.

Chloroquine is the cheapest of the malaria drugs, and together with DDT spraying to kill mosquitoes, was expected to help eradicate malaria in the 1950s to 1970s. But resistance to chloroquine developed in the mid-1950s in South-East Asia and in South America in 1959, reaching Africa in the 1970s and 1980s, and now extends over most of the tropical world. In Central America, North Africa and China *P. falciparum* is still sensitive to chloroquine.

David Warhurst, Professor of Protozoal Chemotherapy at the London School of Hygiene and Tropical Medicine, told the *Bulletin*: "It seems clear that this is a very important result. The level of resistance that the mutations [identified in *pfert*] create is low, but it may open the gate to higher resistance by additional mutations."

Exactly how the gene works and how the mutation creates chloroquine resistance is still a puzzle. A malaria parasite feeds on its host's haemoglobin, producing the waste product hemin, which is toxic to the parasite. Normally the hemin is chemically changed into a form the parasite can eliminate. But chloroquine, as well as several other antimalarial drugs, including amodiaquine, quinine, mefloquine and halofantrine, combine with the hemin and interrupt the transformation process, leaving more toxic hemin that kills the parasite. The *pfert* gene seems to make a protein, PfCRT, which sits on the wall of the parasite's stomach, or food vacuole, and affects the acidity of the stomach contents, which in turn may interfere with how chloroquine combines with hemin. Alternatively, the protein may affect how much chloroquine enters the parasite's stomach.

"Only further research will tell us exactly what *pfert* and its mutations do, but its discovery changes the foundations for thinking about the whole process of chloroquine resistance," Dr Wellems told the *Bulletin*. "There have been dozens of different theories, but now we have a specific molecule, PfCRT, to focus on."

Three years ago, the NIAID group reported that another gene, called *cg2*, was linked to parasite resistance to chloroquine. "This gene, however, was not clearly associated with chloroquine resistance in South America, and has now been ruled out as the cause of chloroquine resistance," Dr Wellems said. "There is far more evidence pointing to the *pfert* gene, which seems to

be linked to chloroquine resistance in Africa, Asia and Latin America."

The discovery of *pfert* holds promise for new drugs, according to Dr Wellems. "If we can mimic the action of chloroquine with another drug that blocks the *pfert* resistance mechanisms, it should have a long life."

Dr Wellems' team included David A. Fidock of the Albert Einstein College of Medicine, in New York, and Paul D. Roepe, of Georgetown University. ■

Robert Walgate, *London*

First countries to be recipients of GAVI funds

The Global Fund for Children's Vaccines has named the first 21 countries to receive funding for vaccines and vaccination infrastructure. They are Armenia, Azerbaijan, Bhutan, Cambodia, Côte d'Ivoire, Ghana, Guyana, Haiti, Kenya, Kyrgyzstan, the Lao People's Democratic Republic, Liberia, Madagascar, Malawi, Mali, Mozambique, Pakistan, Rwanda, Sao Tomé and Príncipe, Uganda, and the United Republic of Tanzania. These countries will get US\$ 250 million over the next five years.

The fund, which was established through an initial gift of US\$ 250 million from the Bill and Melinda Gates Foundation, is administered by the Global Alliance for Vaccines and Immunization (GAVI). It aims to bring its total resources to US\$ 1.8 billion over the next five years. So far it has raised closed to US\$ 1 billion.

About 98% of the fund's resources go directly to countries' immunization programmes. The first awards, a GAVI statement says, should enable the 21 recipient countries to immunize four million children against hepatitis B. A further 600 000 children, who would otherwise not have received any vaccines, will be immunized against childhood diseases common in these countries. Altogether about 100 000 lives will be saved every year, GAVI estimates, thanks to these first grants.

GAVI, which is an alliance of multi-lateral and bilateral agencies, foundations, the vaccine industry, technical organizations and international organizations — among them UNICEF, the World Bank, the Rockefeller Foundation and WHO — was launched in January this year to speed up the development and use of vaccines in poor countries.

“Never before have we been able to provide this level of assistance directly to countries in such a short time,” said WHO Director-General Gro Harlem Brundtland, who also chairs the GAVI board. “It is unacceptable that 30 million children today are not fully vaccinated.”

The Global Fund aims to provide funding over the next two years to all 74 countries in the world with a per capita GNP of less than US\$ 1000. Countries applying must provide five-year plans attesting to increased government commitment to vaccines and vaccination. The amount of support a country gets from the Fund depends on the extent to which it meets its vaccination goals: every newly immunized child, for example, earns for the country one “share” worth US\$ 20 in Global Fund support. The country must use part of that support to strengthen routine immunization and part to introduce newer but under-used vaccines, such as those against hepatitis B and *Haemophilus influenzae* type b (Hib).

“This new approach — issuing an open call to eligible countries and asking them to design improved immunization programmes based on local needs and conditions — is clearly resonating among donors and developing country officials,” said UNICEF Director Carol Bellamy, also a member of the GAVI Board. ■

John Maurice, *Bulletin*

Doctors' first strike in Republic of Korea likely to end

Doctors in the Republic of Korea voted by a narrow margin on 20 November to end a four-month long strike that has brought the country's health care system virtually to a standstill, but divisions within their ranks suggest that further confrontation is possible in the future. The ballot comes after the Korean Medical Association reached a tentative compromise agreement with the government and pharmacists earlier in November over medical reforms.

This industrial action, the first in the history of the Association, began mid-year in protest against a new law that attempted to draw a clear boundary between the prescription and dispensation of drugs and to end a decades-old system believed to be unique to the Republic of Korea. Under this system, there has been considerable overlap between doctors, who could sell medicine, and pharmacists, who could

recommend and sell a wide range of professional drugs.

By separating the two, the government aims to cut the misuse and overuse of drugs, which many health experts in the Republic of Korea believe may be the reason why the country has one of the highest antibiotic resistance rates in the world.

Although the principle of separation has been accepted by all parties, its implementation on 1 August sparked a violent struggle. Doctors, who earned up to half of their incomes from drug sales, insist that the government compensate them by raising consultancy fees. They also demand tougher penalties for pharmacists who sell professional drugs without a doctor's prescription or prepare and sell alternative remedies for out-of-stock medicines. Pharmacists are opposed to a tightening of restrictions on the range of drugs they can sell.

The pattern of the industrial action has been different for each category of doctor. General practitioners have staged five one-week strikes and they are now back at work. The majority of residents and interns, however, have been on strike continuously since the end of July, according to the Korean Medical Association. At the peak of the industrial action, the Association says all of its 70 000 members were on strike, though they operated a rota system to ensure that emergency rooms, intensive care units and delivery rooms were kept open. All but the most urgent surgery has been postponed. According to national media, several patients have died because they were unable to receive treatment, though the Association and the government deny that the struggle has led to any fatalities. At least one doctor has been seriously injured in clashes with riot police.

At the beginning of November, the Korean Medical Association stepped up its protest. More than 80% of interns and residents refused to operate even for emergency cases. Many university hospitals had to call in professors to carry out emergency operations.

However, hopes for a resolution rose by 11 November, when the three conflicting parties reached a compromise to revise the Pharmaceutical Affairs Law. Under the agreement, pharmacists will be banned from making up substitute medicines without a doctor's consent. To beef up regulation of the industry, the government has promised to establish a task force to

crack down on over-the-counter sales of professional drugs.

In the 20 November ballot, doctors voted by 48% to 47% in favour of the proposed revision of the medicines law. Opponents of the revision are demanding a recount. But Dr Doyen Cho of the Korean Medical Association believes “there is little chance of another strike this year.”

The Korean Medical Association said they were uncertain whether their rank-and-file members would accept the deal, but they were aware that public opinion was turning against them. “The doctors' credibility has fallen significantly because of this miserable strike. They can no longer command the respect in society that they once had,” said Dr Choi Hee-ju, director of the health resources policy division of the health ministry. “I don't know who won or lost, but this will certainly prove a turning point for the Korean health-care system.” ■

Jonathan Watts, *Tokyo*

WHO's plan for Internet health domain halted

At its meeting in Los Angeles in mid-November the board of the Internet Corporation for Assigned Names and Numbers (ICANN), the body that manages the labels or "domains" people use to identify their Internet sites, did not give the go-ahead to a WHO proposal for a new "top-level" domain for health. If accepted, the proposal, WHO believes, would have made it easier for people to find reliable health information on the Web.

Top-level domains are the three-letter labels that come at the end of an Internet site's address and denote the type of activity of the site owner. Up to now there had been only seven top-level domains, and they had reigned unchallenged over the past two decades. The three commonest top-level domains — ".com" (commercial firms), ".net" (networking companies) and ".org" (non-profit organizations) — are used by more than 24 million sites (vs only 7000 in 1992 and an expected 160 million by 2003).

ICANN decided in June to open the gates to proposals for new top-level domains. It received 47 applications, covering a variety of sites. Each applicant has to pay a US\$ 50 000 fee but, if accepted, can collect fees from anyone registering a web site on its domain. At its meeting, the ICANN board decided to accept seven new top-level domains identifying businesses, business cooperatives, information, the aviation industry, museums, professionals and individuals. At this writing, the reasons for ICANN's failure to accept WHO's proposal for a ".health" top-level domain are not known. Apparently, the board did not formally reject the proposal but set it aside for later consideration, together with more than 100 others.

WHO issued a statement reiterating its conviction that "the quality and standard of health information on the Internet can only benefit from a ".health" top-level domain". It stated its intention to continue to try and achieve this objective.

WHO's proposed ".health" domain would be restricted: that is, its use would be confined to those agreeing to abide by certain rules and standards agreed upon after wide consultation between WHO

and other players in the health arena. The domain's "sponsor", in this case WHO, would have responsibility to check on whether applicants or users of the domain were providing health information up to the agreed standards.

"The idea," WHO's Joan Dzenowagis told the *Bulletin*, "is to make it easier for Internet users to find trustworthy information on health. There are currently about 10 000 sites on health and the user has no way of telling how reliable the information on them is. At the same time we want to raise the overall standards and protect people from misleading or even dangerous information on health."

Dr Dzenowagis, who first came up with the idea for a ".health" domain, is a scientist with WHO's Department of Health Information Management and Dissemination. ■

John Maurice, *Bulletin*

A second WHO region declared polio-free

On October 29, a panel of independent experts meeting in Japan declared WHO's Western Pacific Region free of poliomyelitis. The declaration, made by the region's commission for the certification of polio eradication, signifies that no indigenous cases — as distinct from imported cases — of the disease have occurred over the past three years. The last case in the region was that in a 15-month-old girl in Cambodia, paralysed by the disease in March 1997.

China, the biggest country in the region, last year reported a case of polio in its remote Qinghai province, that turned out not to be indigenous but due to an imported virus — imported in all probability from northern India. A major emergency operation to prevent its spread from this case cost the Chinese government and donor agencies about US\$ 14 million.

With its 37 countries accounting for a quarter of the world's population, the Western Pacific now joins the 800 million inhabitants of WHO's Region of the Americas — declared polio-free in 1994 — in leading the march towards global certification of eradication of the disease, set for 2005. The European Region, which has reported no new cases in almost two

years, is expected to add its 51 countries and nearly 900 million inhabitants to the polio-free club in just over a year. More than half of the world's population will then be officially free of the disease, leaving 20 countries, mainly in Africa — West and Central, and the Horn of Africa — and parts of Asia, still striving to rid themselves of the virus.

Massive immunization campaigns are under way to vaccinate more than 200 million children in Afghanistan, Bangladesh, India, Nepal and Pakistan, and about 70 million children in 17 countries in Africa where poliovirus is still circulating.

Since WHO launched the global drive to eradicate polio in 1988, cases have dropped steadily year by year from an estimated 350 000 in 1988 to 7094 reported in 1999 and only 1481 reported so far this year, as of this writing. ■

John Maurice, *Bulletin*