fetal infections, maternal thyroid and nutritional deficiencies, placental disorders, and genetic diseases including Prader-Willi and Angelman's syndromes, Rett's syndrome, myotonic dystrophy, non-ketotic hyperglycinaemia, thrombophilic disorders, brain malformations, and family history of epilepsy.[4–9] In the Western Australian study, 28% of infants with encephalopathy had birth defects compared with 4% of controls, and these defects were judged to have contributed to the encephalopathy in 37% of these cases.[10]

The relative distribution of causes for encephalopathy may differ by region of the world and level of medical care. Although the incidence of moderate or severe encephalopathy in newborn babies reported in recent case-control studies from Western Australia and Nepal was identical (3·8/1000 term livebirths), 60% of term infants with encephalopathy in Nepal had intrapartum asphyxia or other intrapartum risk factors, by contrast with less than 30% of cases from Western Australia.[4,5] Mortality associated with encephalopathy in Nepal was also threefold higher than in Western Australia (31% *vs* 9·1%). However, both studies reported that maternal thyroid disorders and infection were major antepartum risk factors for neonatal encephalopathy.

What has been lacking in previous studies is modern MRI of the brain during the neonatal period. The large series reported in this issue of *The Lancet* by Frances Cowan and colleagues from two centres in the UK and Netherlands answers this need and suggests that this modality is useful. In the total series of 351 infants, 77% had evidence of acute hypoxic ischaemic lesions, focal infarctions, or haemorrhages, but only 1% had evidence of old lesions on imaging or autopsy. One interesting feature of the study was the high rate of focal infarctions or haemorrhages in infants with seizures who did not meet other criteria for encephalopathy (69% of 90 infants). Although most investigators and studies such as the Western Australian study have generally lumped infants with seizures alone into a group with other signs of encephalopathy, Cowan and colleagues split their patients into two groups: one with signs of encephalopathy (abnormal tone, feeding, and alertness plus signs of fetal distress) with or without seizures, and another with seizures but no other signs of encephalopathy. The seizure-only group was especially likely to have arterial strokes, and of this group 30% had thrombophilic disorders including factor V Leiden mutation or a high factor VIII concentration. This group also included 31% with identifiable metabolic, neurocutaneous, vascular, or genetic developmental disorders. Imaging also revealed genetic diagnoses in eight patients in the group with encephalopathy. For nearly all these patients, MRI provided information that was useful for management. Biagioni et al,[11] including some of the investigators from today's study, found in an earlier smaller series of cases that MRI also appears to be useful for predicting neurological outcome, especially when combined with electroencephalography.

Cowan's new study is important because of its size and demonstration of the power of MRI, but its design limits the epidemiological conclusions that can be reached about the relative contribution of antenatal versus intrapartum causes of encephalopathy. Because it was not population-based, as was the Western Australian study, referral bias could have influenced selection of patients. In addition, the study excluded patients with disorders such as fetal alcohol syndrome, neural tube defects, other malformations, and chromosome defects that were included in the broader entry criteria of the Western Australian study. Although less common than hypoxic and ischaemic lesions in the Cowan study, the variety of important and unexpected infectious, genetic, metabolic, and thrombophilic diagnoses detected by imaging underscores once again the need to consider a broad group of diagnoses beyond intrapartum asphyxia in newborn infants with encephalopathy.

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To treat or not to treat? Implementation of DOTS in Central Asia

Walk through one of the overcrowded tuberculosis hospitals in Karakalpakstan, Uzbekistan, and the reality of the devastation wreaked by this global pandemic is all too apparent. A high incidence of tuberculosis (new case notification rate 261/100 000 per year) exacts a heavy toll on a population already suffering the economic and environmental effects of one of the worst man-made disasters of the twentieth century: the desiccation of the Aral Sea.[1] Médecins Sans Frontières arrived in the region in 1997, and began a DOTS (directly observed treatment, short course) treatment programme in collaboration with local tuberculosis services. However, in Uzbekistan only the lucky get DOTS. Only 7% of Uzbekistan's population are covered by the DOTS strategy.[2] Indeed, globally, WHO has recently acknowledged that the pace of DOTS expansion has fallen below expectation. The 70% case-detection target will now not be reached until 2013, not 2000 as originally planned.[3]

The unlucky in Uzbekistan, and much of Central Asia, still receive treatment under the pre-DOTS Soviet-style treatment system. Once a strong system, the break-up of the former Soviet Union in 1991 sent the health services of the Central Asian states into rapid decline.[4] Treatment now involves widely varying and often inadequate drug

regimens, and an intermittent drug supply that forces many to purchase drugs at unregulated local bazaars: exactly the conditions under which multidrug-resistant tuberculosis is created.[5] Nowhere is the need to rapidly expand the DOTS programme more evident than in this part of the world.

However, implementation of DOTS is far from straightforward. In the field, expert opinion is conflicting and clear guidance is lacking about how to provide the most appropriate treatment with maximum benefits. Two of the five key pillars of the DOTS strategy—directly observed therapy and diagnosis by smear microscopy—are tricky to implement in the face of a dispersed population and poorly paid, poorly motivated staff with continued allegiance to a deteriorating Soviet system. Discussion about the pace of DOTS expansion in such a context is fundamental. Many argue that these problems are impediments to expansion; that expansion should only happen when all the conditions are exactly right, assessed by reaching the WHO target of 85% success for new smear-positive cases.[6] However, this argument is invalid in Central Asia, where high rates of multidrug-resistant tuberculosis render reaching this target impossible[7] and the alternative to DOTS is dangerously inappropriate.

Uzbekistan's failing tuberculosis system is undoubtedly contributing to some of the highest rates of multidrug-resistant tuberculosis yet recorded in the world; 13% of new patients presenting to Médecins Sans Frontières clinics in the Karakalpakstan region have multidrug-resistant tuberculosis. In this context, the introduction of DOTS, with an assured drug supply, standardised regimens, and its effect on the priority given to tuberculosis, is a vast improvement; even with its attendant constraints. Given the constraints, DOTS will prevent the continued large-scale emergence of multidrug-resistant tuberculosis.

In addition to drug resistance, the deteriorating Soviet system has created a large pool of patients who have previously received more than a month of tuberculosis treatment, so-called retreatment cases. These cases make up around half of the smear-positive cases seen in the Médecins Sans Frontières programme and currently less than 10% have received DOTS in the past. Over 40% of these retreatment cases in Karakalpakstan have multidrug-resistant tuberculosis. Of course, over time these cases will gradually be reduced, but the dilemma remains about how to treat them. The WHO manual focuses on treating new cases of tuberculosis and failures of DOTS treatment.[6] There is no guidance about treating infectious patients previously treated with a non-DOTS regimen. Indeed many experts advocate that this group not be included in DOTS at all; at least in the early stages of programmes. The non-inclusion argument is based on the view that to control tuberculosis the priority should be new smear-positive cases, as these cases represent recent transmission. Additionally, by only including new cases, programme success can be used to convince the still sceptical medical community of the effectiveness of DOTS.

But if this argument is followed, half the infectious cases diagnosed do not fall into the category that entitles them to DOTS. Elsewhere in the world, this pool of retreatment cases is smaller, closer to 10% of infectious cases in Benin, for example,[8] and much of Africa. This difference undoubtedly fuels the general confusion and conflicting opinions as to what to do with retreatment patients. In practical terms, to not include retreatment cases would translate on the tuberculosis ward to half the patients receiving a full course of free DOTS and a promise of full recovery but the other half being offered whatever drugs are currently available (including even second-line tuberculosis drugs) in the government system or privately, with a regimen that may or may not work, and which does not enable treatment and outcomes for these patients to be monitored. In effect, such treatment exposes patients to a significant risk of developing multidrug-resistant tuberculosis.

Additionally, the numbers of patients in this category are contributing substantially to tuberculosis transmission. Although 40% of retreatment cases in Karakalpakstan will have multidrug-resistant tuberculosis, for which there is no treatment available at this time, the remaining 60% have a good chance of cure under DOTS, thereby lessening further transmission. Added to this, there is an obligation to treat patients when there is an effective treatment available.

Limiting DOTS expansion and restricting DOTS to only new cases does not offer hope for a rapid and long-lasting solution to the ongoing tuberculosis epidemic in this region. There is an urgent need for context-specific discussion around these issues, a need already acknowledged by WHO,[3] leading to an improved strategy to tackle tuberculosis in areas with high levels of multidrug-resistant disease. This strategy should include appropriate individualised treatment regimens for retreatment cases in this context. Conflicting opinions from experts, a lack of clarity in many areas of the DOTS protocol, and limited international discussion over the practical considerations of treating a disease that is set to kill 30 million people in the next decade[9] leaves those working on the ground unsure of the best way to assist the populations at risk.

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