

## General

### International donor assistance for global malaria control

Most countries in which malaria is endemic will need financial assistance if malaria control targets are to be met. International funding for malaria control has increased in order to attempt to achieve Millennium Development Goal targets but there are still unmet needs. An assessment funded by the Wellcome Trust has been reported.

Since 2007, international financing for malaria control has increased by 166%, from US\$0.73 billion to \$1.94 billion. *Plasmodium vivax* control is less well funded than *Plasmodium falciparum* control. Adequate assistance to provide needed interventions by 2009 has been provided to 21 countries, 12 of them in Africa. Assistance was inadequate, however, in 50 countries (61% of people at risk of malaria) including ten countries in Africa and five in Asia. These countries are among the world's poorest.

The writers of this paper call for more efficient targeting of donations in relation to biological need and national income.

Snow RW et al. Equity and adequacy of international donor assistance for global malaria control: an analysis of populations at risk and external funding commitments. *Lancet* 2010; 376: 1409–16; Mills A. International donor assistance for health. *Ibid*: 1368–70 (comment).

### Kidney function and cardiovascular risk

Two papers in the *BMJ* illustrate the link between kidney function and cardiovascular risk.

A meta-analysis of 21 papers (from 33 prospective studies) included a total of 284 672 patients and 7863 episodes of stroke over follow-up periods of 3.2–15 years. The risk of stroke was increased significantly by 43% among patients with an estimate glomerular filtration rate (eGFR) of <60 ml/min/1.73 m<sup>2</sup>.

A prospective cohort study in Reykjavik, Iceland included 16 958 people with an average follow-up of 24 years. At baseline the prevalence of chronic kidney disease was 7% (1210 participants) and none of the participants had manifest cardiovascular disease. Those with chronic kidney disease had a 55% to 4.3-fold increase in adjusted risk of coronary disease compared with participants with a normal eGFR and no proteinuria, the risk increasing with the severity of the kidney disease. Chronic

kidney disease was also associated with a 26% increase in risk of non-vascular, non-cancer mortality. The association between chronic kidney disease and coronary disease was not as strong as the links between diabetes or smoking and coronary disease.

Chronic kidney disease should be taken into account when assessing cardiovascular risk.

Lee M et al. Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ* 2010; 341: 767 (c4249); Di Angelantonio E et al. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population-based cohort study. *Ibid*: 768 (c 4986); Perkovic V, Cass A. Glomerular filtration rate and the risk of stroke. *Ibid*: 739–40 (c 4390) (editorial).

### Educating women reduces child mortality

Education is important for national development and has been reported to be associated with improvements in health indicators. Survey data from 175 countries for the period 1970–2009 have illustrated the strong link between improved education of women and reduced child mortality.

During this period the mean number of years of education increased overall from 4.7 to 8.3 for men and from 3.5 to 7.1 for women. In developing countries the average length of schooling among women of reproductive age (15–44 years) increased from 2.2 to 7.2 years. In 87 countries by 2009 women aged 25–34 years were better educated than men. Deaths among children under the age of 5 years fell by 8.2 million between 1970 and 2009 and it is estimated more than half of this improvement could be attributed to better education of women.

Better education of women leads to empowerment of women, better earning power, increased uptake of health services, and a marked reduction in child mortality.

Gakidou E et al. Increased educational attainment and its effect on child mortality in 175 countries between 1970 and 2009: a systematic analysis. *Lancet* 2010; 376: 959–74; The *Lancet*. Equity as a shared vision for health and development. *Ibid*: 929 (editorial); Cleland J. The benefits of educating women. *Ibid*: 933–4 (comment).

### Worldwide availability of operating theatres and pulse oximetry

About 234 million surgical operations are done around the world each year; 75% of them in the richest third of the world population and 4% in the poorest third. An estimation has been made of the world distribution of operating the-

atres and of pulse oximeters.

Profiles from 769 hospitals in 92 countries in seven geographical regions were used to calculate ratios of operating theatres to hospital beds. The number of operating theatres per 100 000 people were estimated for 21 sub-regions using data from 190 countries. Surveys sent to providers of anaesthesia in 72 countries provided data about pulse oximetry provision. The number of operating theatres per 100 hospital beds ranged from 1.3 in sub-Saharan Africa and 2.0 in Asia to 3.9 in Latin America and 4.5 in North America. The number of operating theatres per 100 000 population ranged from 1.0–1.2 in sub-Saharan Africa and 1.3–11.7 in Asia to 14.3 in North America, 14.7–25.1 in Europe, and 24.3 in the Asia-Pacific region. High-income sub-regions all averaged >14 operating theatres per 100 000 population whereas low-income sub-regions had <2 per 100 000 population. Data from 54 countries suggested that 19% of all operating theatres (77 700 theatres) had no pulse oximeters.

More than 2 billion people worldwide have inadequate access to surgery.

Funk LM et al. Global operating theatre distribution and pulse oximetry supply: an estimation from reported data. *Lancet* 2010; 376: 1055–61; The *Lancet*; what is the point of surgery? *Ibid*: 1025 (editorial); Myles PS, Haller G. Global distribution of access to surgical services. *Ibid*: 1027–8 (comment).

## Cardiology

### Nurse-led interventions for hypertension

A systematic review and meta-analysis has confirmed that nurse-led care using structured algorithms may benefit patients with hypertension.

The review included 33 studies of nurse-led versus usual care for patients with hypertension treated in primary or secondary care clinics. A stepped treatment algorithm was used by nurses in 14 studies and nine studies included nurse prescribing. Compared with usual care, systolic blood pressure was reduced by a mean of 8.2 mmHg in studies using a stepped treatment algorithm. Nurse prescribing was associated with mean reductions of 8.9 mmHg (systolic) and 4.0 mmHg (diastolic) compared with usual care. Telephone monitoring and community monitoring were also successful. Overall, nurse-led clinics in primary care were associated with reductions of 3.5 mmHg in systolic pres-

sure and 1.9 mmHg in diastolic pressure compared with usual care.

Nurse-led care with a structured algorithm is associated with improved blood pressure control.

Clark CE et al. Nurse led interventions to improve control of blood pressure in people with hypertension: systematic review and meta-analysis. *BMJ* 2010; 341: 491 (c 3995).

## Compression only for cardiac arrest

In recent years several studies have shown better results with bystander chest-compression-only resuscitation for out-of-hospital cardiac arrest compared with chest compression plus rescue ventilation (standard cardiopulmonary resuscitation, CPR). Now a meta-analysis has confirmed this benefit.

The primary meta-analysis included three randomised trials (3031 patients). The chance of survival to hospital discharge was 14%, (compression-only) vs 12% (standard), a significant 22% increase with compression only. The number-needed-to-treat was 41. A secondary meta-analysis of seven observational cohort studies showed no difference in outcome between the two methods.

It is suggested that instructions given to bystanders should focus on chest-compression-only CPR. In cardiac arrest from noncardiac causes such as drowning, trauma, or asphyxia (particularly in children) standard CPR may have some advantage.

Hüpfel M et al. Chest-compression-only versus standard cardiopulmonary resuscitation: a meta-analysis. *Lancet* 2010; 376: 1552–7; Nolan JP, Soar J. Dispatcher-assisted bystander CPR: a KISS for a kiss. *Ibid*: 1522

## High-dose simvastatin

Current evidence suggests that the greater the reduction in LDL cholesterol with statin therapy the greater is the reduction in risk of coronary disease. There are concerns, however, about safety at high doses. In a multicentre UK trial doses of simvastatin of 80 mg and 20 mg daily have been compared in myocardial infarction survivors.

The trial included 12 064 patients with a history of myocardial infarction and a total serum cholesterol level of 3.5 mmol/L or greater if already on a statin or 4.5 mmol/L or greater if not. Previous coronary revascularisation had been performed in 3962 patients. Randomisation was to 80 mg or 20 mg of simvastatin daily. Over an average

follow-up of 6.7 years the average reduction in LDL-cholesterol was 0.35 mmol/L greater on 80 mg daily than on 20 mg daily. The rate of the primary end-point (coronary death, myocardial infarction, stroke, or arterial revascularisation) was 24.5% in the 80 mg group and 25.7% in the 20 mg group, a significant 6% proportional reduction with the higher dose. The rates of haemorrhagic stroke and of deaths from vascular or nonvascular causes were similar in the two groups. Myopathy occurred in two patients (0.03%) in the lower-dose group and 53 (0.9%) in the higher-dose group.

In patients with a history of myocardial infarction there was a 6% reduction in risk of major vascular events over an average follow-up of 6.7 years in the 80 mg simvastatin group compared with the 20 mg group. The increase in myopathy could probably be avoided by using other regimens for greater LDL cholesterol reduction such as atorvastatin 80 mg daily, rosuvastatin 20–40 mg daily, or combination regimens.

Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) collaborative group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet* 2010; 376: 1658–69; Cheung BMY, Lam KSL. Is intensive LDL-cholesterol lowering beneficial and safe? *Ibid*: 1622–4 (comment).

## Intensive lowering of LDL cholesterol: meta-analysis

A meta-analysis has provided more information about the effectiveness and safety of intensive lowering of LDL cholesterol levels.

The meta-analysis included individual patient data from five trials (39 612 patients) comparing intensive with less intensive statin regimens and 21 trials (129 526 patients) comparing statins with controls.

When compared with less intensive statin treatment, more intensive statin treatment reduced LDL cholesterol at 1 year by 0.51 mmol/L on average. The accompanying reductions in clinical events were 15% for all major vascular events, 13% for coronary death or non-fatal myocardial infarction, 19% for coronary revascularisation, and 16% for ischaemic stroke. These further risk reductions were similar to the proportional reductions achieved by initiating standard statin therapy. Analysis of data from all 26 trials showed that a 1 mmol/L reduction in LDL cholesterol was associated with a 10% reduction in overall mortality and a 20% reduction in deaths due to coronary

disease. Deaths from stroke, other vascular causes, cancer, or other nonvascular disease were not reduced and cancer incidence was not affected. The benefits applied at all baseline levels of cholesterol, even low levels. An excess of cases of rhabdomyolysis occurred only with simvastatin 80 mg daily.

Intensive cholesterol lowering is effective and safe.

Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 2010; 376: 1670–81; Cheung BMY, Lam KSL. Is intensive LDL-cholesterol lowering beneficial and safe? *Ibid*: 1622–4 (comment).

# Diabetes

## Green leafy vegetables reduce diabetes risk

A systematic review and meta-analysis has addressed the question of whether increased intakes of fruit and vegetables could reduce the risk of type 2 diabetes.

The analysis included six studies (223 512 participants aged 30–74, median follow-up 13.4 years). Four of the studies included only women. Overall, there was no significant effect of increased intake of fruit or vegetables, or both. Increased consumption of green, leafy vegetables, however, was associated with a significant 14% reduction in risk of type 2 diabetes.

Eating more green leafy vegetables could reduce the risk of type 2 diabetes.

Carter P et al. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. *BMJ* 2010; 341: 543 (c 4229); Mann J, Aune D. Can specific fruits and vegetables prevent diabetes? *Ibid*: 514–5 (c 4395) (editorial).

## Severe hypoglycaemia and vascular events

Attempts at intensive glucose control in patients with diabetes increase the risk of severe hypoglycaemia, which may have an adverse effect on cardiovascular outcomes. Analysis of data from the ADVANCE trial reported in 2007 and 2008 have shown a strong association between severe hypoglycaemia and adverse outcomes.

The trial included 11 140 patients with type 2 diabetes and was a factorial trial with randomisation to perindopril-indapamide vs placebo for blood pressure lowering and to intensive glucose lowering vs standard glucose control for vascular outcomes. Over an average

follow-up of 5 years 231 patients (2.1%) had at least one episode of severe hypoglycaemia (blood glucose <2.8 mmol/L and unable to self-treat because of the hypoglycaemia). The rate of severe hypoglycaemia was 2.7% in the intensive glucose control group and 1.5% in the standard control group. During follow-up severe hypoglycaemia was associated with a significant 2.9-fold increase in risk of major macrovascular events, a significant 80% increase in risk of major microvascular events, a significant 2.7-fold increase in risk of cardiovascular death, and a significant 2.7-fold increase in risk of death from any cause. There were also significant increases in risk of respiratory, digestive, and skin conditions. Repeated severe hypoglycaemia did not affect the associations.

Severe hypoglycaemia may contribute to adverse outcomes or it may be a marker of vulnerability.

Zoungas S et al. Severe hypoglycaemia and risks of vascular events and death. *NEJM* 2010; 363: 1410–8.

## Tropical

### Artesunate versus quinine in Africa

In Africa, severe malaria is usually treated with quinine but studies in Asia have suggested that artesunate might be better. Now a trial in nine sub-Saharan countries has confirmed the superiority of artesunate for children with severe falciparum malaria.

At 11 centres in Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and Democratic Republic of the Congo a total of 5425 children with severe falciparum malaria were randomised to i.v. or i.m. artesunate or quinine. Mortality was 8.5% (artesunate) vs 10.9% (quinine), a highly significant 25% reduction with artesunate compared with quinine. Coma, convulsions, and deterioration in coma score were all significantly less frequent in the artesunate group. Post-treatment hypoglycaemia occurred in 1.8% vs 2.8%. Artesunate was well tolerated.

It is suggested that parenteral artesunate should become standard treatment for severe falciparum malaria in all countries.

Dondorp A M et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* 2010; 376: 1647–57; Shanks GD. For severe malaria, artesunate is the answer. *Ibid*: 1621–2.

## Infection

### Hepatitis E vaccine

Around the world probably one in three people have been infected with hepatitis E virus. Most cases occur in developing countries but it is also possibly the most common cause of acute viral hepatitis in developed countries. The severity is greater in older people and in around 1–3% of cases it is fatal. It does not usually give rise to chronic hepatitis. In pregnant women mortality is high (5–25%) and spontaneous abortion and stillbirth are common. Superinfection with hepatitis E virus in patients with chronic liver disease worsens the prognosis. An epidemic in Uganda has been associated with high mortality (13% in children with the disease). Now a trial of a recombinant vaccine in China has shown it to be effective and safe.

The trial included 112 604 healthy adults aged 16–65 years who were randomised to vaccine (HEV239, consisting of purified recombinant hepatitis E antigen adsorbed to aluminium hydroxide suspended in buffered saline) or placebo, each given i.m. in three doses at 0, 1, and 6 months. Among 11 165 people tested, 47% were seropositive for hepatitis E virus. During the 12 months beginning 30 days after the last vaccine dose 15 patients given three doses of placebo and none given three doses of vaccine developed hepatitis E. Vaccine efficacy after three doses was therefore 100%. The vaccine was well tolerated with no serious adverse events.

The HIV 239 vaccine was effective and apparently safe.

Zhu F-C et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010; 376: 895–902; The Lancet. Hepatitis E vaccine: why wait? *Ibid*: 845 (editorial); Holmberg SD. Hepatitis E vaccine: not a moment too soon. *Ibid*: 849–51 (comment)

### Rapid test for pulmonary tuberculosis and rifampicin resistance

A rapid, simple, point-of-treatment test for the diagnosis of tuberculosis and antituberculous drug resistance might save many lives by eliminating delays in appropriate treatment. A fully automated molecular test for the diagnosis of pulmonary tuberculosis and rifampicin (rifampin) resistance (Xpert MTB/RIF) has been assessed in a trial at five sites on four continents.

The study included 1730 adults with

suspected pulmonary tuberculosis, drug sensitive or multidrug resistant, at five sites in Lima, Peru; Baku, Azerbaijan; Cape Town and Durban, South Africa; and Mumbai, India. Three sputum samples were tested from each patient. Two of the three samples were processed with N-acetyl-L-cysteine and sodium hydroxide before Ziehl-Neelsen staining and microscopy, tuberculosis culture on solid and liquid media, and testing with the MTB/RIF test. The third sample was subjected to Ziehl-Neelsen microscopy and the MTB/RIF test without the above processing. Among patients with a positive culture result the single direct MTB/RIF test identified 551/561 (98.2%) patients with smear-positive tuberculosis and 124/171 (72.5%) patients with smear-negative tuberculosis. There were five false positives in 609 patients without tuberculosis. Among smear-negative, culture-positive patients doing a second MTB/RIF test increased sensitivity to 85.1% and doing three increased it to 90.2%. Compared with conventional drug-susceptibility testing, the MTB/RIF test correctly identified 97.6% of rifampicin-resistant cases and 98.1% of rifampicin-sensitive cases. For multidrug resistance (to both rifampicin and isoniazid) the sensitivity was 97.5%. The results of the MTB/RIF test were available in <2 hours.

The MTB/RIF test was sensitive and specific and gave rapid results. It is more costly than microscopy but probably less costly than setting up culture and drug-sensitivity testing.

Boehme CC et al. Rapid molecular detection of tuberculosis and rifampin resistance. *NEJM* 2010; 363: 1005–15. Small PM, Pai M. Tuberculosis diagnosis - time for game change. *Ibid*: 1070–1 (editorial).

### Active case-finding for tuberculosis in Zimbabwe

In Africa, tuberculosis is often the result of recently acquired disease resulting from casual contact rather than the remotely acquired infection transmitted by close household contact seen in rich countries. Therefore, community case-finding should result in reduced prevalence. Researchers in Zimbabwe have compared two strategies for active case-finding: door-to-door surveys and use of a mobile van with a loudspeaker.

In suburban Harare, 46 community clusters (41 419 households, 110 432 adults aged 16 years or older) were randomised to door-to-door (DTD) or mobile van (MV) groups. Six rounds of active case-finding were carried out at

6-month intervals in 2006–2008. The prevalence of HIV infection was 21%. Before the intervention the tuberculosis smear-positivity rate was 2.8 per 1000 adults per year. In the MV group there were 255 smear-positives in 5466 participants and in the DTD group 137 in 4711 participants, a significant difference. Overall, the prevalence of culture-positive tuberculosis fell from 6.5 to 3.76 cases per 1000 adults.

Active case finding could rapidly reduce the prevalence of tuberculosis. In this study use of a mobile van was more effective than door-to-door visiting. *Lancet* commentators stress the importance of efforts to develop a rapid, accurate, and simple test for tuberculosis.

Corbett EL et al. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *Lancet* 2010; 376: 1244–53; Getahun H, Ravigione M. Active case-finding for TB in the community: time to act. *Ibid*: 1205–6 (comment).

## AIDS

### Antiretroviral treatment for mother and child after single-dose nevirapine

Single-dose nevirapine given to the mother in labour and to the child after birth reduces the risk of mother-to-child HIV transmission but it promotes nevirapine resistance. Successive papers in the *New England Journal of Medicine* address the question of optimum antiretroviral therapy for mothers after single-dose nevirapine and for children who acquire HIV infection despite the prophylaxis.

Two trials were performed in seven countries in sub-Saharan Africa. Trial 1 included 241 women who had had single-dose nevirapine and trial 2 included 500 women who had not. Randomisation in each trial was to tenofovir-emtricitabine plus nevirapine (TEN) or tenofovir-emtricitabine plus lopinavir and low-dose ritonavir (TELr). In trial 1 the primary end-point (virological failure or death) occurred in 26% of the TEN group and 8% of the TELr group. Virological failure occurred in 23% vs 8% and death without virological failure in 3% vs <1%. The advantage of TELr over TEN became less as the time between receiving single-dose nevirapine and starting full antiretroviral therapy increased. The baseline prevalence of nevirapine resistance

was 14%. In trial 2 14% in each group reached the primary end-point.

In a trial in six countries in sub-Saharan Africa a total of 164 children aged 6–36 months who had become infected with HIV despite single-dose nevirapine prophylaxis were randomised to zidovudine-lamivudine plus nevirapine (ZLN) or zidovudine-lamivudine plus lopinavir and low-dose ritonavir (ZLLr). The primary end-point (virological failure or treatment discontinuation by study week 24) was reached by 40% (ZLN) vs 22% (ZLLr), a significant difference.

Resistance to nevirapine at baseline was detected in 12% of the children. After single-dose nevirapine prophylaxis antiretroviral treatment was better with a regimen not including nevirapine. New regimens for prophylaxis and treatment are needed.

Lockman S et al. Antiretroviral therapies in women after single-dose nevirapine exposure. *NEJM* 2010; 363: 1499–509; Palumbo P et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *Ibid*: 1510–20; Lallemand M, Jourdain G. Preventing mother-to-child transmission of HIV-protecting this generation and the next. *Ibid*: 1570–2.

### PRO2000 vaginal gel to prevent HIV infection: negative trial

PRO2000 is a synthetic naphthalene sulfonate polymer that has been shown to have anti-HIV activity in laboratory and animal experiments. Now a phase 3 clinical trial has shown that PRO2000 vaginal gel is not effective as a prophylactic against HIV-1 infection.

In South Africa, Tanzania, Uganda, and Zambia a total of 9385 sexually active, HIV-negative women aged 16 years or older were randomised to 2% PRO2000, 0.5% PRO2000, or placebo gel for 52 weeks. The primary efficacy analysis included 8859 women. An average of 84% of women reported using the allocated gel at last sex act. The incidence of HIV-1 infection was 4.7 per 100 woman-years (2% PRO2000), 3.9 per 100 woman-years (0.5% PRO2000), and 3.9 per 100 woman-years (placebo) up to the time of discontinuation of use of the 2% PRO2000 gel after review by the independent monitoring committee. The incidence of an adverse event of grade 3 or worse was 4.5, 4.6, and 3.9 per 100 women-years in the three groups respectively.

PRO2000 vaginal gel was safe but not effective. *Lancet* commentators point to tenofovir gel and conditional (or unconditional) cash transfer to relieve poverty in young women as more promising approaches to reducing rates of HIV infection.

McCormack S et al. PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): a phase 3, randomised, double-blind, parallel-group trial. *Lancet* 2010; 376: 1329–37; McCoy SI et al. Preventing HIV infection: turning the tide for young women. *Ibid*: 1281–2 (comment).

## Paediatrics

### Infant diet and beta-cell autoimmunity

Evidence of beta-cell autoimmunity may precede the onset of type 1 diabetes by several years. Brief or no breast feeding and early exposure to complex dietary proteins may increase the risk of type 1 diabetes and there is some evidence from experimental models that early dietary intervention may be protective. Now a trial in Finland has shown that dietary modification in infancy may inhibit the development of markers of beta-cell autoimmunity. A total of 230 newborn infants with an HLA genotype associated with increased risk of type 1 diabetes and at least one first-degree relative with the disease were randomised to receive a hydrolysed casein-based formula (nutramigen) or a control formula (20% hydrolysed milk protein) whenever breast milk was not given in the first 6–8 months of life, although breast feeding was encouraged for all mothers. Follow-up was for 10 years. Blood was taken at 3, 6, 9, 12, 18, and 24 months and at 3, 5, 7, and 10 years and autoantibodies to insulin, glutamic acid decarboxylase (GAD), the insulinoma-associated 2 molecule (IA-2), zinc transporter 8, and islet cells were measured. At least one of these antibodies developed in 17% (experimental group) vs 30% (controls) and at least two in 8% vs 16%. After adjustment for duration of exposure to the study formula the risk of positivity for at least one autoantibody was reduced by 49% in the experimental group compared with controls and of positivity for at least two autoantibodies by 53%.

Dietary intervention in infancy may prevent or delay the development of diabetes-associated autoantibodies. Editorialists point to difficulties in interpreting the data. Knip M. Et al. Dietary intervention in infancy and later signs of beta-cell autoimmunity. *NEJM* 2010; 363: 1900–8; Harlan DM, Lee MM. Infant formula, autoimmune triggers, and type 1 diabetes. *Ibid*: 1961–3 (editorial).

### Apgar score and cerebral palsy

In infants born at term a low Apgar score at 5 minutes after birth is associated with an increased risk of cerebral palsy but

the association is less clear in preterm infants. A study in Norway has confirmed an association at all birthweights.

All babies born in Norway between 1986 and 1995 were identified from the national Medical Birth Registry and children with cerebral palsy were identified from the national cerebral palsy registry. The study included 543 064 children born during this period without congenital malformations who survived for at least a year. A diagnosis of cerebral palsy was registered for 988 children. Overall, the prevalence of cerebral palsy was 39/369 (10.6%) among children with an Apgar score of <3 and 162/179515 (0.09%) among children with an Apgar score of 10, a 53-fold increase after adjustment for birthweight. The risk decreased with increasing birthweight. Apgar scores of <4, 4–6, 7–8, and >8 were associated with cerebral palsy risks of 16.9%, 10.0%, 10.1%, and 4.2% among children with a birthweight <1500g; 11.3%, 4.7%, 2.9%, and 0.8% at birthweights of 1500–2499g; and 9.7%, 2.3%, 0.3%, and 0.1% at birthweights of 2500g or greater. The association between low Apgar score and cerebral palsy applied to all types of cerebral palsy but most strongly to quadriplegia.

There is an association between low Apgar score and cerebral palsy at all birth weights but most children with cerebral palsy had a normal Apgar score.

Lie KK et al. Association of cerebral palsy with Apgar score in low and normal birthweight infants: population based cohort study. *BMJ* 2010; 341: 817 (c4990); Paneth N. Apgar score and risk of cerebral palsy. *Ibid*: 788–9 (c 5175) (editorial).

### Official development assistance for maternal, newborn, and child health

Only a minority of developing countries are on track to achieve Millennium Development Goals 4 and 5A for child and maternal health. Lack of financing is often an important factor. Official development assistance (ODA) for 2003–2008 has been assessed.

The total disbursement in support of maternal, newborn, and child health agencies in developing countries was US\$4.7 billion in 2007 and \$5.4 billion in 2008. Between 2003 and 2008 the amounts allocated to maternal, newborn, and child health and the overall ODA for health both increased by 105%. Priority countries in the Countdown to 2015 initiative received \$3.4 billion in 2007 and \$4.1 billion in 2008 (71.6% and 75.6% of all maternal, newborn,

and child health disbursements respectively). Between 2002 and 2008 the targeting of ODA to more needy countries improved, but some countries with high maternal and child mortality rates still received less than other countries with lower mortality rates and more money. Funding from the GAVI alliance and the Global Fund to Fight AIDS, Tuberculosis and Malaria was greater than core funding from multilateral institutions. Between 2003 and 2008 there was a substantial increase in bilateral funding especially from the USA and the UK.

ODA funding has improved but ODA for maternal, newborn, and child health has not increased more than for other areas of health. A *Lancet* commentator discusses priorities and need in ODA allocations, whether some more rapidly developing countries still need so much ODA, and the roles of ministries of health.

Pitt C et al. Countdown to 2015: assessment of official development assistance to maternal, newborn, and child health, 2003–08; *Lancet* 2010; 376: 1485–96; Sridhar D. Improving aid for maternal, newborn, and child health. *Ibid*: 1444–6 (comment).

## Oncology

### ALK inhibition with crizotinib for some non-small-cell lung cancers

Activating mutations or translocations affecting the anaplastic lymphoma kinase gene (*ALK*) have been found in cancers including anaplastic large-cell lymphoma, neuroblastoma, inflammatory myofibroblastic tumour, and non-small-cell lung cancer. An oncogenic fusion gene (*EML4-ALK*) is present in 2–7% of non-small-cell lung cancers and is more likely in patients who have never smoked and in adenocarcinomas. In vitro experiments have shown that an *ALK* inhibitor reduces the proliferation of human cancer cells that carry *ALK* mutations. A phase 1 multicentre trial of crizotinib, an *ALK* inhibitor, in patients with non-small-cell lung cancers with mutated *ALK* has been reported.

About 1500 patients with non-small-cell lung cancer were screened and 82 had advanced disease with *ALK* rearrangements. These 82 patients were on average younger than the other patients, had usually smoked lightly or not at all, and mostly had adenocarcinoma (79 patients). They were treated with crizotinib 250mg twice daily in 28-day cycles. With a mean treatment duration of 6.4 months there was a complete response

in one patient and 46 had a partial response. The disease stabilised in 27 patients (33%). At the time of data analysis 63 patients were still taking crizotinib. The estimated probability of 6-month progression-free survival was 72%. There were mild gastrointestinal side-effects.

Crizotinib was effective in patients with advanced non-small-cell lung cancer with *ALK* rearrangement.

Kwak EL et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *NEJM* 2010; 363: 1693–703; Hallberg B, Palmer RH. Crizotinib – latest champion in the cancer wars? *Ibid*: 1760–2.

### More on crizotinib

Two more papers (see above) in the *New England Journal of Medicine* report the use of crizotinib and the development of crizotinib resistance.

The first report concerns two patients with inflammatory myofibroblastic tumour (IMT), a mesenchymal neoplasm usually affecting the lung, retroperitoneal tissues, or the abdomen and the pelvic region in patients in the first two decades of life. One patient, a man aged 44 years, had tumours in the abdomen and pelvis that showed *ALK* rearrangement. After surgery he was treated with chemotherapy followed by imatinib but the disease recurred and he then received crizotinib 200mg twice daily. Three months later the size of the lesions had reduced by 53%. The maximum response was at 6–7 months but several lesions then enlarged. After further surgery and restarting treatment with crizotinib at a dose of 250mg twice daily complete radiographic remission was achieved and was still maintained 21 months later. On treatment he experienced leg oedema and joint pains and developed hypocalcaemia, hypophosphataemia, leukopenia, and anaemia, all of them mild.

The second patient was a 21-year-old man whose IMT presented with jaundice and vomiting and was multinodular – affecting the region of the head of the pancreas and the walls of the stomach and colon – and was *ALK*-negative. He did not respond to crizotinib. The second report describes a 28-year-old never-smoking man with an *ALK*-positive lung adenocarcinoma that progressed on chemotherapy. On treatment with crizotinib his symptoms improved rapidly and there was a partial tumour response but after 5 months the tumour began to grow again. Treatment was stopped and further investigation revealed two secondary mutations within the kinase domain of the *EML4-ALK* fusion oncoprotein. Each

of these variants conferred marked resistance to ALK inhibitors.

ALK inhibition may be effective treatment for some patients with non-small-cell lung cancer and some other cancers but resistance may develop.

Butrynski JE et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. *NEJM* 2010; 1727–33; Choi YL et al. *EML4-ALK* mutations in lung cancer that confer resistance to ALK inhibitors. *Ibid*: 1734–9; Hallberg B, Palmer RH. Crizotinib – latest champion in the cancer wars? *Ibid*: 1760–2 (editorial).

## Gastrology

**Lifestyle and colorectal cancer risk**  
A study in Denmark has confirmed that lifestyle factors affect the risk of colorectal cancer.

A total of 55487 participants aged 50–64 years were enrolled in the Diet, Cancer and Health Cohort Study in Copenhagen and Aarhus in 1993–1997 and average follow-up was for 10 years. Colorectal cancer developed in 678 participants. A lifestyle index was calculated for each participant, based on physical activity, waist circumference, smoking, alcohol intake, diet, and anthropometry. For each 1-point increase (improvement) in lifestyle index, due to following one additional lifestyle recommendation, there was an 11% fall in incidence of colorectal cancer, a 12% fall in colon cancer and an 11% fall in rectal cancer. It was calculated that 13% of cases of colorectal cancer could have been prevented if all participants had taken up one extra lifestyle recommendation. In the population as a whole 23% of cases of colorectal cancer might be attributable to lack of adherence to lifestyle recommendations.

Lifestyle changes could reduce the incidence of colorectal cancer appreciably.

Kirkegaard H et al. Association of adherence to lifestyle recommendations and risk of colorectal cancer: a prospective Danish cohort study. *BMJ* 2010; 341: 978 (c5504); Bekker JL. Decision aids and uptake of screening. *Ibid*: 948–9 (c5407) (editorial).

### New drugs for chronic hepatitis C

More than 170 million people are infected with hepatitis C virus and 1 in 5 of them will develop cirrhosis. Currently treatment of chronic hepatitis C is with s.c. pegylated interferon alfa and oral ribavirin but a combination drug treatment that did not include interferon might be more effective and better tolerated. A combination of two new oral drugs RG

7128, a nucleoside polymerase inhibitor, and danoprevir, a protease inhibitor) has been assessed in New Zealand and Australia.

A total of 88 patients aged 18–65 years with chronic hepatitis caused by hepatitis C virus (HCV) genotype 1 were randomised to one of seven treatment groups (up to 13 days of RG 7128 plus danoprevir at doses of 500 or 1000 mg of RG7128 twice daily and 100 or 200 mg of danoprevir every 8 hours or 900 mg twice daily), or a placebo group. The median change in HCV RNA concentration from baseline to day 14 ranged from -3.7 to -5.2 log<sub>10</sub> IU/ml in the treatment groups and was +0.1 log<sub>10</sub> IU/ml in the placebo group. At doses of 1000 mg of RG7128 and 900 mg of danoprevir twice daily the median change was -5.1 log<sub>10</sub> IU/ml in treatment-naive patients and -4.9 log<sub>10</sub> IU/ml in previous standard of care null responders. The combination treatment was well tolerated with no treatment-related serious or severe adverse events. All patients were treated with pegylated interferon and ribavirin after the experimental treatment.

This drug combination merits further investigation as a non-interferon-containing treatment for chronic hepatitis C. Gane EJ et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG 7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. *Lancet* 2010; 376: 1467–75; Thomas DL. Curing hepatitis C with pills: a step toward global control. *Ibid*: 1441–2 (comment).

## Psychology

### Antipsychotic drugs and venous thromboembolism

Case reports and small studies have suggested that antipsychotic drug treatment may be associated with an increased risk of venous thromboembolism (VTE). A large population-based, case-control study using routinely collected data from 453 UK general practices has confirmed the association.

The study included 25532 cases (15975 with deep vein thrombosis and 9557 with pulmonary embolism) and 89491 matched controls. The prescription of an antipsychotic drug within the last 24 months was associated with a 35% increase in risk of VTE after adjustment for risk factors. The risk was greater (a two-fold increase compared with non-users) among patients who had begun treatment in the last 3 months. Atypical

antipsychotic drugs in the previous 24 months were associated with a 70% increase in risk compared with a 28% increase with conventional drugs. The increase in risk was greater (99%) with low potency drugs than with high potency drugs (28%). Treating 10000 patients for 1 year would result in four extra cases of VTE overall and 10 extra cases if all the patients were aged 65 or older.

Antipsychotic drug therapy is associated with increased risk of VTE especially within the first 3 months of treatment, with use of atypical or low potency drugs, and in older patients.

Parker C et al. Antipsychotic drugs and risk of thromboembolism: nested case-control study. *BMJ* 2010; 341: 641 (c 4245); Liperoti R, Gambassi G. Antipsychotics and the risk of venous thromboembolism. *Ibid*: 613–4 (c 4216) (editorial).

### Intimate-partner violence in pregnancy and postnatal depression

Reported rates of violence against women in pregnancy by intimate male partners vary from 3% in London to 4–8% in the USA, and 31% in Mexico City. Several studies have suggested a link between such violence and postnatal depression but there have been methodological problems with those studies. Now a study in Brazil has illustrated the importance of psychological violence in particular.

The prospective cohort study included 1045 pregnant women between July 2005 and December 2006. They were aged 18–49 years, in the third trimester of pregnancy and attending primary healthcare clinics. Interviews were carried out during and after pregnancy using a validated questionnaire to assess psychological, physical, and sexual violence and the Edinburgh postnatal depression scale to diagnose postnatal depression. This diagnosis was made in 270 women (26%). The prevalence of psychological violence was 28%, physical violence 12%, and sexual violence 6%. After appropriate adjustments, women who reported many episodes of psychological violence were 2.3 times more likely to develop postnatal depression than were women who reported no psychological violence. The effects of psychological violence were independent of those of physical or sexual violence.

Psychological violence in pregnancy is strongly associated with postnatal depression.

Ludermir AB et al. Violence against women by their intimate partner during pregnancy and postnatal depression: a prospective cohort study. *Lancet* 2010; 376: 903–10; Jewkes R. Emotional abuse: a neglected dimension of partner violence. *Ibid*: 851–2