General

Lower limits of beneficial exercise

Guidelines have recommended a target of at least 150 min of exercise per week to maintain good health. Many people find this amount of exercise difficult to achieve and people in east Asia tend to be less physically active than in Western countries. Researchers in Taiwan have tried to assess the minimum amount of exercise that is beneficial.

The study, between 1996 and 2008, included 416 175 people (216 910 women) aged 20 years or older and the average follow-up was 8 years. Weekly exercise volume was assessed by questionnaire and participants were classified into five categories: inactive, low, medium, high, or very-high exercise. Individual types of exercise were classed as light (e.g. walking), moderate (brisk walking), medium–vigorous (jogging), or high–vigorous (running), and metabolic equivalent values (METs) were derived (1 MET = 1 kcal per hour per kg bodyweight). Low-volume exercise for 92 min per week was associated with a 14% reduction in all-cause mortality, a 10% reduction in cancer mortality, a 20% reduction in cardiovascular mortality, and a 3-year increase in life expectancy compared with inactivity. Every additional 15 min of exercise per day above the minimum of 15 min was associated with a further reduction in all-cause mortality of 4% and a reduction in cancer mortality of 1%.

It is suggested that people should aim to do at least 15 min a day (or 90 min a week) of moderate intensity exercise.

Wen CP et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet* 2011; 378: 1244–53; Nigam A, Juneau M. Survival benefit associated with low-level physical activity. Ibid: 1202–3 (comment).

Smoking and tuberculosis worldwide

Smoking tobacco increases the likelihood of tuberculosis and death from the disease. A mathematical modelling analysis has illustrated the problem of smoking and tuberculosis worldwide.

It was estimated that smoking would cause 18 million extra cases of tuberculosis globally between 2010 and 2050 (256 million cases without smoking, 274 million with smoking). Deaths from tuberculosis were estimated at 61 million without smoking and 101 million with smoking. Smoking would be responsible for a 64% increase in tuberculosis mortality in Europe and a 135% increase in the eastern Mediterranean. Because of smoking, the Millennium Development Goal for tuberculosis (reduction of 50% in prevalence and mortality between 1990 and 2015) will not be met in the Americas, eastern Mediterranean, South East Asia, and Western Pacific regions of the World Health Organization (WHO). It was estimated that reduction of smoking prevalence by 1% a year in each WHO region from 2015, and eventual eradication of smoking, would reduce tuberculosis cases by 239 million and tuberculosis deaths by 74 million between 2015 and 2050 (13% and 27% reductions). A doubling of the present rate of increase in smoking prevalence (up to a prevalence of 50%) would result in a 6% rise in cases of tuberculosis and a 12% rise in deaths from tuberculosis between 2015 and 2050.

Tobacco control would be a substantial aid to tuberculosis control.

Basu S et al. Projected effects of tobacco smoking on worldwide tuberculosis control: mathematical modelling analysis. *BMJ* 2011; 343: 733 (d5506).

BMI, abdominal circumference, and mortality among black women in the USA

The prevalence of obesity has increased rapidly in the USA with the greatest increase being in black women. The Black Women's Health Study is a cohort study of 59 001 black women aged 21–69 at enrolment in 1995. Data about obesity and mortality on follow-up to 2008 have been reported for the 33 916 women who never smoked.

During follow-up 770 of the 33 916 women died. Mortality was lowest at BMI values of 20.0 to 24.9. With this BMI range as the reference range, mortality was increased by 12%, 31%, 27%, 51%, and 119% at BMIs of 25.0, to 27.4, 27.5 to 29.9, 30.0 to 34.9, 35.0 to 39.9, and 40.0 to 49.9. Among women with a BMI of at least 20.0, each 5-unit increase in BMI was associated with an 18% increase in mortality. BMIs of <18.5 and 18.5 to 19.9 were associated with 89% and 36% increases in mortality, compared with the reference group. For waist circumference the reference range was 26.0 to 27.0 in. A waist circumference of 28.0 to 29.0 in. was associated with a 5% increase in mortality and a waist circumference of 40 to 47 in. was associated with a 75% increase relative to the reference range.

Among women with a waist circumference of at least 26 in, a 5-unit increase in waist circumference was associated with a 12% increase in mortality after adjustment for BMI. This was significant only among nonobese women.

Boggs DA et al. General and abdominal obesity and risk of death among black women. *NEJM* 2011; 365: 901–8.

Cytisine to help smoking cessation

Strategies that have been shown to be helpful in aiding smoking cessation include behavioural support and drug treatment. In poorer countries, however, the cost of treatment may exceed that of cigarettes. Cytisine is extracted from Golden Rain acacia seeds (*Cytisus laborinum L.*) and has been used as an aid to quitting smoking in former socialist economy (FSE) countries such as Russia, Bulgaria, and Poland, for many years. It is a partial agonist with high affinity binding to the α4β2 subtype of the nicotinic acetylcholine receptor that has been implicated in nicotine dependence. Now a study at a single centre in Warsaw, Poland has shown that cytisine is more effective than placebo in promoting smoking cessation.

A total of 740 smokers (at least 10 cigarettes a day and willing to try to stop) were randomised to cytisine or placebo for 25 days, with minimal counselling. The rate of biochemically verified abstinence for 12 months was 8.4% (cytisine) vs 2.4% (placebo), a highly significant difference. The 7-day point prevalence for abstinence at the 12-month follow-up was 13.2% vs 7.3%. Gastrointestinal adverse events were more common in the cytisine group.

Cytisine was more effective than placebo. Compared with other drugs used for smoking cessation it is relatively inexpensive and may be affordable in developing countries.

West R et al. Placebo-controlled trial of cytisine for smoking cessation. *NEJM* 2011; 365: 1193–200.

Cardiology

Hourly changes in air pollution and myocardial infarction risk

Chronically increased exposure to air pollution is associated with increased risk of myocardial infarction. The effects of short-term changes in exposure are not well studied. A study at 15 urban locations in England and Wales has suggested that short-term (hourly) changes do not have a large effect on the risk of

myocardial infarction.

The study included retrospective data about 79 288 people who had a myocardial infarction in 2003–2006. The air pollutants measured were particulate matter (PM10), ozone, carbon monoxide (CO), nitrogen dioxide (NO_2), and sulphur dioxide (SO_2). Exposure levels were averaged from hourly measurements over five short-lag periods spanning 72 hours. For each patient exposure on the day of myocardial infarction was compared with data on every other day in the same calendar month. For PM10 a 10 µg per m3 increase in air pollution was associated with a significant 1.2% increase in risk of myocardial infarction 1–6 hours later but this was followed by a reduction in risk so that the risk in the 72 hours after exposure was not increased. The results were similar for a 10 µg per m3 increase in NO_2. Increases in CO, ozone, or SO_2 were not followed by increases in risk of myocardial infarction.

Short-term increases in PM10 or NO_2 were followed by increased risk of myocardial infarction over the next 6 hours. There was however a subsequent fall in risk so that the 72-hour risk was not increased, suggesting that the increased pollution precipitated events that would have occurred within the next few hours or days in any event.

Short-term increases in PM10 and NO_2 are associated with 'short-term displacement' of myocardial infarction events.

Bhaskaran K et al. The effects of hourly differences in air pollution on the risk of myocardial infarction: case-crossover analysis of the MINAP database. *BMJ* 2011; 343: 626 (d5531); Hales S, Edwards R. Cardiovascular effects of exposure to air pollution. Ibid: 595–6 (d5814) (editorial).

Ambulatory monitoring: best way to diagnose hypertension

Blood pressure levels from ambulatory monitoring correlate better with cardiovascular outcomes than do clinical measurements. In general practice ambulatory modelling may not be available immediately; it may be inconvenient; and its cost-effectiveness is unknown. In a UK study, Markov model-based probabilistic cost-effectiveness analysis has been used to assess three strategies: repeated blood pressure measurements in the clinic, home monitoring, and ambulatory monitoring. The study used a hypothetical primary-care population aged 40 years or older with screening blood pressure of >140/90 mmHg and risk factors equivalent to the general population. The most cost-effective strategy was ambulatory monitoring. The cost saving from ambulatory monitoring varied from £56 in men aged 75 to £323 in women aged 40. It preserved more QUALYs (quality adjusted life years) than the other strategies for both men and women over the age of 50.

Ambulatory monitoring after a raised clinic reading is cost-effective. The costs of ambulatory monitoring are more than balanced by savings from better-directed treatment. These researchers suggest that all patients should have ambulatory monitoring before starting antihypertensive treatment.

Lovibond K et al. Cost-effectiveness of options for the diagnosis of high blood pressure in primary care: a modelling study. *Lancet* 2011; 378: 1219–30; Gaziano TA. Accurate hypertension diagnosis is key to efficient control. Ibid: 1199–200 (comment).

Secondary drug prophylaxis for cardiovascular disease worldwide

Beta blockers, ACE inhibitors, statins, and antiplatelet drugs are all effective as secondary prophylaxis after a cardiovascular event. Other hypertensive drugs may also add to prophylaxis. Although most cardiovascular disease occurs in low- or middle-income countries the extent to which drug prophylaxis is used in those countries is unknown. A worldwide study has shown that the use of secondary prophylactic drugs is low everywhere, but especially in low-income countries.

The study included 153 996 people in 628 communities in 17 countries (three high-income, ten middle-income, and four low-income). A total of 5650 participants had had a coronary event and 2292 had had a stroke, on average 4 or 5 years previously. Among people with cardiovascular disease, antiplatelet drugs were taken by 25%, β blockers by 17%, ACE inhibitors or ARBs by 20%, and statins by 15%. In high-income countries the corresponding proportions were 62% (antiplatelet drugs), 40% (β blockers), 50% (ACE inhibitors or ARBs), and 67% (statins). In low-income countries the proportions were 9% (antiplatelet drugs), 10% (β blockers), 5% (ACE inhibitors or ARBs), and 3% (statins). No drugs were taken by 11% in high-income countries, 45–69% in middle-income countries, and 80% in low-income countries. Drug use was lower in rural than in urban areas and this gap was greatest in low-income countries. In determining the rate of prophylactic drug use country-level factors (national economic status) were more important than individual-level factors (age, sex, education, smoking status, BMI, hypertension, diabetes).

The use of secondary drug prophylaxis is low in most countries but lowest in the poorest countries. Efforts need to be made to extend its use.

Yusuf S et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet* 2011; 378: 1231–43; Heagerty AM. Secondary prevention of heart disease and stroke: work to do. Ibid: 1200–2 (comment).

Surgery

Anaemia at the time of major surgery and outcomes

Although preoperative anaemia is associated with increased morbidity and mortality after cardiac surgery, its effect on outcomes of major non-cardiac surgery remain uncertain. Now data from 211 hospitals worldwide in 2008 have shown that preoperative anaemia is associated with worse outcomes after major non-cardiac surgery.

Data were obtained for 2008 from the American College of Surgeons' National Surgical Quality Improvement Program database. A total of 227 425 surgical patients (mean age 56 years) were included, 30% of whom had preoperative anaemia (haematocrit <36% for women or <39% for men). Mortality at 30 days was increased by 42% (after statistical adjustment) among patients with preoperative anaemia. This finding was similar with mild or moderate-to-severe anaemia. Postoperative morbidity (cardiac, respiratory, CNS, urinary tract, wound, sepsis, or venous thromboembolism) was 35% higher among anaemic patients. Anaemia increased the risks associated with other risk factors and anaemia alone was also associated with increased risk.

Preoperative anaemia, either mild or moderate-to-severe, increases postoperative mortality and morbidity among patients undergoing major noncardiac surgery.

Musallam KM et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet* 2011; 378: 1396–407; Gombotz H. Patient blood management is key before elective surgery. Ibid: 1362–3 (comment).

Long-term results of epilepsy surgery in adults

There has been only one randomised controlled trial of epilepsy surgery and that showed that anterior temporal lobe resection was in the short term, better

than medical treatment for refractory temporal lobe epilepsy. A rate of freedom from seizures at 10 years of 41% has been reported after anterior temporal lobe resection. Now workers at the National Hospital for neurology and Neurosurgery in London have reported the long-term outcomes of various forms of epilepsy surgery at their hospital.

The study included 615 adults who had undergone anterior temporal resection (497), temporal lesionectomy (40), extratemporal lesionectomy (40), extratemporal resection (20), hemispherectomy (11), and palliative procedures (corpus callosotomy, subpial transection) (7). Follow-up was annually for 1–19 years (median 8 years). Altogether 52% remained seizure-free (apart from simple partial seizures) at 5 years after surgery and 47% at 10 years. Seizure recurrence was twice as common after extratemporal resection as after anterior temporal resection. After lesionectomy the results were similar to those after anterior temporal resection. Simple partial seizures in the first 2 years after operation were associated with a 2.4-fold increase in risk of subsequent seizures with impaired awareness. A longer seizure-free period predicted a lower rate of relapse and at the latest follow-up 28% (104/365) seizure-free patients had discontinued drug treatment. Introduction of a new antiepileptic drug induced late remission in 18 of 93 people (19%).

Surgery may provide long-term benefit for about half of selected adults with refractory epilepsy. Children need separate consideration.

de Tisi J et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet* 2011; 378: 1388–95; Sadek A-R, Gray WP. Chopping and changing: long-term results of epilepsy surgery. Ibid: 1360–2 (comment).

Obs & Gyn

Women exposed to diethylstilbestrol in utero: more on adverse health outcomes

It has been known for 40 years that diethylstilbestrol (DES) given to mothers during pregnancy induces clear-cell adenocarcinoma of the vagina and cervix in their daughters in adolescence and early adulthood. Later, developmental defects of the genital tract and complications of pregnancy were added to the long-term effects. Now three US cohort studies combined have provided more long-term data.

Altogether, the three studies, with follow-up to an average age of 48 years, included 4653 women exposed to DES in utero and 1927 unexposed controls. The risks of 12 outcomes were assessed in exposed women and controls up to the age of 45 for reproductive outcomes and 55 for other outcomes. The risks for all 12 outcomes were increased in exposed women compared with controls. The rates for exposed women vs controls and hazard ratios were: infertility, 33.3% vs 15.5% (2.37); spontaneous abortion, 50.3% vs 38.6% (1.64); ectopic pregnancy, 14.6% vs 2.9% (3.72); loss of second trimester pregnancy, 16.4% vs 1.7% (3.77); preterm delivery, 53.3% vs 17.8% (4.68); pre-eclampsia, 26.4% vs 13.7% (1.42); stillbirth, 8.9% vs 2.6% (2.45); neonatal death, 2.4% vs 0.56% (8.12); early menopause 5.1% vs 1.7% (2.35); cervical intraepithelial neoplasia grade 2 or greater, 6.9% vs 3.4% (2.28); breast cancer at age 40 years or older, 3.9% vs 2.2% (1.82); and clear-cell adenocarcinoma, 0.09% vs 0.0% (infinity). Vaginal epithelial changes at baseline increased the risk of most outcomes.

The daughters of women who took DES in pregnancy have increased lifetime risks for a wide range of adverse outcomes.

Hoover RN et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. *NEJM* 2011; 365: 1304–14.

Polycystic ovary syndrome: adverse pregnancy outcomes

The incidence of polycystic ovary syndrome has been reported as 3–15% of women of reproductive age. The features include hyperandrogenism, anovulation, and polycystic ovaries. Meta-analyses have shown that the condition is associated with increased risks of gestational diabetes, pre-eclampsia, preterm birth, and perinatal mortality. It has been unclear, however, whether the risks are due to the polycystic ovary syndrome itself or to the associated features such as obesity or fertility treatments with increased risk of multiple pregnancy. Now a study in Sweden has shown that polycystic ovary syndrome is associated with adverse pregnancy outcomes irrespective of the use of assisted reproductive technology.

Using national birth and patients registers data were obtained for all singleton births in Sweden between 1995 and 2007. There were 1 195 123 births and in 3787 cases the mother had polycystic ovary syndrome. The risks of adverse pregnancy outcomes (gestational diabetes, pre-eclampsia, low Apgar score, meconium aspiration, small or large for gestational age, macrosomia) were adjusted for maternal characteristics, socioeconomic factors, and use of assisted reproductive technology. Comparing women with polycystic ovarian syndrome with women without the syndrome: affected women were more likely to be obese (61% vs 35%) and to have used assisted reproductive technology (14% vs 2%). They were 45% more likely to have pre-eclampsia, 2.2 times more likely to have very preterm delivery, and 2.3 times more likely to have gestational diabetes. Among their infants there was a 39% increase in largeness for gestational age, a two-fold increase in meconium aspiration, and a 40% increase in low Apgar score at 5 minutes.

Women with a diagnosis of polycystic ovary syndrome are at increased risk of adverse pregnancy outcomes irrespective of whether they have used assisted reproductive technology or not.

Roos N et al. Risk of adverse pregnancy outcomes in women with polycystic ovary syndrome: population based cohort study. *BMJ* 2011; 343: 835 (d6309); Macklon NS. Polycystic ovary syndrome. Ibid: 804–5 (d6407) (editorial).

Tropical

Blood-stage malaria vaccine trial

Vaccines aimed at the blood stages of malaria could reduce morbidity and mortality from the disease and add to the possibility of developing a multi-antigen vaccine that attacks the parasite at several stages. The vaccine FMP2.1/AS02A is a monovalent blood-stage vaccine based on apical membrane antigen 1 (AMA1) from the 3D7 *Plasmodium falciparum* strain. A proof-of-concept trial has been performed in Mali.

A total of 400 children aged 1–6 years were randomised to receive the malaria vaccine or rabies vaccine (controls) and followed for 6 months. The primary endpoint (clinical malaria with fever and at least 2500 parasites per cu mm of blood) occurred in 48.4% (malaria vaccine) vs 54.4% (controls), giving an efficacy against this outcome of 17.4% (nonsignificant). The efficacy against malaria caused by parasites with the vaccine strain of AMA1 was 64.3% (significant). The vaccine caused local reactions and fever.

The vaccine was effective against the

specific AMA1 strain of parasite. It could form part of a multicomponent vaccine.

Thera MA et al. A field trial to assess a blood-stage malaria vaccine. *NEJM* 2011; 365: 1004–13.

Malaria and bacteraemia in children

Bacteraemia is common in children in sub-Saharan Africa. HIV infection, malnutrition, and sickle-cell disease all contribute to the susceptibility. Malaria is also thought to make children susceptible to invasive bacterial infections. Sickle-cell trait (HbAs), however, provides protection against malaria, and researchers in Kenya have taken advantage of this to perform a mendelian randomisation study.

First, they studied 292 children aged 3 months to 13 years with bacteraemia and 528 control children. Bacteraemia was associated with sickle-cell disease, HIV infection, undernutrition, and leukocyte haemozoin pigment. Sickle-cell trait was associated with a 64% reduction in risk of bacteraemia. Next, they performed a longitudinal case-control study with 1454 cases (children with bacteraemia) and 10749 controls. Between 1999 and 2007 the rate of hospital admission for malaria fell from 28.5 to 3.45 admissions per 1000 child-years because of more effective malaria control. At the same time the protection provided by sickle-cell trait against bacteraemia fell and hospital admissions for bacteraemia, largely Gram-negative bacteraemia including cases due to non-typhoidal salmonella, decreased in parallel with those for malaria, from 2.59 to 1.45 per 1000 child-years. Malaria parasitaemia increased the risk of bacteraemia 6.7-fold. In 1999, the prevalence of parasitaemia in the community was 29% and 62% of cases of bacteraemia were attributed to malaria.

Malaria control should reduce the prevalence of bacteraemia.

Scott JAG et al. Relation between falciparum malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study. *Lancet* 2011; 378: 1316–23; Obaro S, Greenwood B. Malaria and bacteraemia in African children. Ibid: 1281–2 (comment).

Pulmonary

COPD: small airway obstruction and emphysema

In chronic obstructive pulmonary disease (COPD) the main site of airway obstruction is in the small airways (<2 mm internal diameter). High resolution computed tomography (CT) has shown that in the lungs of people with severe COPD, the areas with emphysematous destruction show a reduced number of airways. Now researchers in Canada and the USA have reported further CT studies that may lead to changes in the definition of emphysema.

The study included 78 patients at different stages of COPD who were studied using multidetector CT. The isolated lungs from patients with COPD who had undergone lung transplantation and donor (control) lungs were also examined. Micro CT was used to assess the extent of emphysema, the number of terminal bronchioles per ml of lung volume, and the minimum diameters and cross-sectional areas of terminal bronchioles. On multidetector CT the number of airways measuring 2.0 to 2.5 mm in diameter was reduced in patients with stages 1 to 4 COPD compared with controls. Lung samples from patients with stage 4 disease showed reductions of between 81% and 99.7% in the total cross-sectional area of terminal bronchioles and of 72–89% in the number of terminal bronchioles. The narrowing and loss of terminal bronchioles happened before emphysematous destruction.

Narrowing and disappearance of small conducting airways occurs before the onset of emphysematous destruction and explains the increase in peripheral airway resistance in COPD.

McDonagh JE et al. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *NEJM* 2011; 365: 1567–75; Mitzner W. Emphysema – a disease of small airways or lung parenchyma? Ibid: 1637–9 (editorial).

Change in FEV1 with time among patients with COPD

There is a paucity of data about the rate of decline of forced expiratory volume in 1 second (FEV1) among patients with chronic obstructive pulmonary disease (COPD). A multinational study has shown a high degree of variability in this rate of decline with more rapid deterioration in some patient subgroups.

The study included a total of 2163 patients who had FEV1 measured after taking a bronchodilator, 1–8 times over a 3-year period. The mean rate of decline in FEV1 was 33 ml per year. A decline of >40 ml per year was recorded in 38% of patients and of 21–40 ml per year in 31%. A change ranging from a decline of 20% to an increase of 20% in FEV1 per year was recorded in 23% and an increase of >20 ml per year in 8%. The rate of decline among current smokers was greater than that in current non-smokers by 21.4 ml per year. Patients with emphysema had a 13 ml per year greater decline than patients without emphysema and reversibility with a bronchodilator was associated with a 17.4 ml per year faster decline compared with nonreversibility.

The rate of decline in FEV1 is highly variable among patients with COPD. The patients at highest risk of rapid decline are current smokers, patients with emphysema, and patients whose bronchoconstriction responds to a bronchodilator. The latter finding is unexplained. Some patients may have static or even improving disease. Stopping smoking is the most important factor in slowing or preventing the decline

Vestbo J et al. Changes in forced expiratory volume in 1 second over time in COPD. *NEJM* 2011; 365: 1184–92; Burney P. Variable loss of function in COPD. Ibid. 1246–7 (editorial).

Genetics of nonresponsiveness to inhaled steroid in people with asthma

There is a wide variation in responsiveness to inhaled steroid among people with asthma. A genomewide association study in the USA has pointed to a single-nucleotide polymorphism (SNP) in the Glucocorticoid-induced transcript 1 gene (GLCCI1) as being responsible for nonresponsiveness to inhaled steroid.

The study included 403 parent-child units (each of mother, father, and child) from a previous trial of treatment in asthma. A total of 534290 autosomal SNPs were available for analysis and the 100 most likely SNPs were chosen for evaluation. Patient data were obtained from five clinical trials in all. An association was found between two SNPs in GLCCI1 (rs 37972 and rs 37973) and reduced GLCCI1 expression, and the rs 37973 SNP was associated with reduced luciferase reporter activity. Pooled data from the five treatment trials showed reduced response to inhaled steroid in patients with this variant allele. The mean increase in FEV1 with treatment in patients homozygous for the variant was 3.2%, whereas among patients homozygous for the wild-type (nonmutant) allele it was 9.4%. A poor response to treatment was 2.4 times more likely with the mutant SNP. Genotype accounted for 6.6% of all variability of response to inhaled steroid.

The variant in GLCCI1 was associated

with poor response to inhaled steroid in people with asthma.

Tantisira KG et al. Genomewide association between GLCCI1 and response to glucocorticoid therapy in asthma. *NEJM* 2011; 365: 1173–83; Drazen JM. A step toward personalized asthma treatment. Ibid: 1245–6 (editorial).

AIDS

Effect of point-of care CD4 cell testing on management and outcomes in Mozambique

Although more patients in developing countries are receiving antiretroviral therapy (ART) around two-thirds of HIV-infected patients who need ART still remain untreated. Loss to follow-up is common and is highest (up to 80%) between diagnosis and initiation of treatment. Point-of-care CD4 cell testing might reduce this loss to follow-up. A trial in Mozambique has shown that such testing led to increased use of ART.

At four public primary health clinics point-of-care CD4 testing was introduced in March–April 2010. The proportion of patients lost to follow-up before CD4 staging fell from 57% before point-of-care CD4 testing to 21% with the testing. The rate of loss to follow-up before treatment fell from 64% to 33% and the proportion of patients who started ART increased from 12% to 22%. The median time from enrolment to beginning ART fell from 48 days to 20 days and the median time to complete CD4 staging fell from 32 days to 3 days.

The introduction of point-of-care CD4 testing reduced the time to complete CD4 staging, reduced the rate of loss-to-follow up during that time, and increased the uptake of ART.

Jani IV et al. Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in primary health clinics: an observational cohort study. *Lancet* 2011; 378: 1572–9; Kassaye SG, Katzenstein D. The point of point-of-care testing. Ibid: 1532–3 (comment).

HIV and tuberculosis: timing of initiation of antiretroviral therapy

There is uncertainty about the best time to start antiretroviral therapy (ART) in patients infected with HIV and tuberculosis. The main reason for starting ART soon after beginning antituberculosis therapy is quicker restoration of immunocompetence with better response to antituberculosis therapy and increased protection against opportunistic infections. Reasons given for delaying ART include increased drug toxicity, increased risk of the immune reconstitution inflammatory syndrome (IRIS), and adding to the number of pills with increased risk of nonadherence to treatment. Three successive papers in the *BMJ* have addressed this problem.

A multicentre trial in Cambodia included 661 adults with HIV infection, no previous ART, a CD4+ T-cell count of 200 per cu mm or lower, and newly diagnosed tuberculosis. Randomisation was to commence ART (stavudine, lamivudine, and efavirenz) either 2 weeks or 8 weeks after beginning a standard 6-month course of treatment for tuberculosis. The median CD4+ count was 25 per cu mm and median viral load 5.64 log10 copies per ml. The median duration of follow-up was 25 months. Mortality was 59/332 (18%) with earlier ART and 90/329 (27%) with later ART, a significant 42% reduction with early ART. There were 110 IRIS events in the early ART group and 45 in the later ART group giving rates of 3.76 vs 1.53 cases per 100 person-months, a significant 2.5-fold increase with early ART. By week 50 CD4+ counts had risen similarly in both groups and 96.5% of patients had no detectable viral load with no difference between groups. There was no increase in drug toxicity in the early ART group.

A study at 26 sites on four continents included 809 patients with a median CD4+ cell count of 77 per cu mm and viral load of 5.43 log10 copies per ml. Death or a new AIDS-defining illness occurred within 48 weeks in 12% of the early (within 2 weeks) ART group and 16.1% of the later (within 8–12 weeks) ART group, a nonsignificant difference. Among patients with a baseline CD4+ count <50 per cu mm, however, the corresponding figures were 15.5% vs 26.6%, the difference just failing to reach significance (P=0.06). Tuberculosis-associated IRIS was more common in the early ART group (11% vs 5%).

In South Africa, a total of 429 patients were randomised to early (within 4 weeks of starting antituberculosis treatment) or later (within 4 weeks of completing the intensive phase of antituberculosis treatment) ART. Overall, the incidence of AIDS or death was 6.9 per 100 person-years (early ART) vs 7.8 per 100 person-years (later ART), a nonsignificant difference. Among patients with an initial CD4+ count of <50 per cu mm, the corresponding figures were 8.5 vs 26.3 cases per 100 person-years, a significant 68% reduction with early ART.

An editorialist concludes that the evidence supports early initiation of ART in patients with HIV, advanced immunosuppression, and tuberculosis, unless they have tuberculous meningitis when early ART may be associated with increased mortality and severe IRIS.

Blanc F-X et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *NEJM* 2011; 365: 1471–81; Havlir DV et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. Ibid: 1482–91; Abdool Karim SS. Integration of antiretroviral therapy with tuberculosis treatment. Ibid: 1492–501; Török ME, Farrar JJ. When to start antiretroviral therapy in HIV-associated tuberculosis. Ibid: 1538–40 (editorial).

Paediatrics

Vitamin A supplements for children in developing countries: systematic review and meta-analysis

A systematic review and meta-analysis has confirmed the value of vitamin A supplements given to children in developing countries.

The study included 16 trials (194 483 children aged 6 months to 5 years). Vitamin A supplementation was associated with a 24% reduction in mortality. There was a significant 28% reduction in diarrhoea mortality and a nonsignificant 20% reduction in measles mortality. There were significant reductions in prevalence of Bitot's spots of the bulbar conjunctiva (by 55%), night blindness (by 68%), and xerophthalmia (by 69%).

Vitamin A supplementation for children aged 6 months to 5 years reduces the incidence of diarrhoea and overall mortality. It also results in significant reductions in the features of vitamin A deficiency and might prevent blindness from this cause.

Mayo-Wilson E et al. Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: systematic review and meta-analysis. *BMJ* 2011; 343: 519 (d5094); Thorne-Lyman A, Fawzi WW. Improving child survival through vitamin A supplementation. Ibid: 487–8 (d5294) (editorial).

Adjuvanted influenza vaccine for children

Many countries recommend seasonal influenza vaccination for children but the trivalent inactivated vaccine (TIV) produces poor immune responses in young children. Now the addition of MF59, an oil-in-water emulsion, as an adjuvant to TIV has been shown to increase the immunogenicity of TIV and to give greater efficacy.

A total of 4707 children aged 6 to <72

months were randomised to TIV without adjuvant, TIV with adjuvant (ATIV), or a control (non-influenza) vaccine. The vaccines were given as two doses, with an interval of 28 days, during the influenza seasons of 2007–2008 and 2008–2009 in Germany and 2008–2009 in Finland. The rates of influenza-like illness were 0.7% (ATIV), 2.8% (TIV), and 4.7% (controls) and the vaccine efficacy rates against all influenza strains were 86% (ATIV) and 43% (TIV). Among children aged 6 to <36 months the efficacy was 79% (ATIV) and 40% (TIV). Among children aged 36 to <72 months the corresponding efficacies were 92% and 45%. The antibody titres achieved were greater with ATIV. There were more systemic reactions with ATIV in the older children. The rate of adverse reactions was similar in all three groups.

ATIV was more efficacious than TIV in infants and young children.

Vesikari T et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. *NEJM* 2011; 365: 1406–16.

Millennium goals 4 and 5: an update on progress

The targets for Millennium Development Goals (MDGs) 4 and 5 are a reduction in under-5s mortality by two-thirds and in maternal mortality ratio by three-quarters between 1990 and 2015. A further update on progress has been reported using recent surveys, censuses, vital registration, and verbal autopsy data.

It is estimated that under-5 deaths will have fallen to 7.2 million in 2011 with 2.2 million early neonatal deaths, 0.7 million late neonatal, 2.1 million postneonatal infantile, and 2.2 million of children aged 1–4 years. The rate of decline of under-5s mortality was greater in 2000–2011 than in 1990–2000 in 106 countries. There has been no progress towards MDG4 in four countries. Maternal mortality has fallen from 409 100 in 1990 to 273 500 in 2011. In 2011, it is estimated that 56 100 maternal deaths will be HIV-related. Twenty developing countries show no progress towards MDG5. Current estimates suggest that 31 countries will achieve MDG4, 13 will achieve MDG5, and 9 will achieve both targets. Fourteen countries are likely to achieve both targets by 2020. *Lancet* commentators question the value of frequent, differing estimates of progress. Most developing countries will not achieve the targets of MDG4 and MDG5 until many years after 2015.

Lozano R et al. Progress towards Millennium Development Goals 4 and 5 on maternal and child mortality: an updated systematic analysis. *Lancet* 2011; 378: 1139–65; Byass P, Graham WJ. Grappling with uncertainties along the MDG trail. Ibid: 1119–20.

Infection

HPV vaccination to prevent anal disease

Anal cancer has biological similarities to cervical cancer and a similar relationship to infection with human papilloma virus (HPV). The development of anal cancer is preceded by high-grade anal intraepithelial neoplasia (grade 2 or 3). Prevention or treatment of high-grade anal intraepithelial neoplasia probably prevents, or reduces the incidence of, anal cancer. People at increased risk of anal cancer include men who have sex with men, people of either sex with HIV infection, women with cervical or vulvar cancer, and patients on immunosuppressive treatment after organ transplantation. The quadrivalent HPV vaccine (qHPV) prevents persistent cervical infection with HPV-6, 11, 16, or 18 in women and external genital lesions associated with these HPV types in men. The incidence of anal cancer is increasing in both sexes. A multinational study has shown that qHPV reduces the incidence of anal intra-epithelial neoplasia among men who have sex with men.

A total of 602 of healthy 16–26-year-old men who have sex with men were randomised to qHPV or placebo. The efficacy of qHPV against anal intraepithelial neoplasia associated with HPV types 6, 11, 6 or 18 was 50% (intention to treat analysis) and 77.5% (per protocol analysis). Against anal intraepithelial neoplasia associated with any type of HPV the corresponding efficacies were 26% and 55%. The rates of anal intraepithelial neoplasia in vaccine and placebo groups were 13.0 vs 17.5 per 100 person-years (intention to treat) and 4.0 vs 8.9 per 100 person-years (per protocol). Grade 2 or 3 anal intraepithelial neoplasia related to infection with HPV-6, 11, 16, or 18 was reduced by 54% and 75% and persistent anal infection with these HPV types was reduced by 59% and 95%.

The quadrivalent HPV vaccine reduces rates of anal intraepithelial neoplasia among men who have sex with men. It could reduce the risk of anal cancer.

Palefsky JM et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *NEJM* 2011; 365: 1576–85.

Briakinumab for psoriasis

Acyclovir suppressive therapy after treatment of neonatal herpes

After neonatal herpes simplex virus (HSV) infection the risk of sequelae depends on the initial clinical picture. Superficial disease (skin, eye, and mouth) is associated with a low risk of neurological impairment although there may be skin recurrences. With disseminated disease there is a 30% mortality rate and a 20% risk of neurological damage in survivors. Central nervous system (CNS) infection carries a 6% mortality and a 70% risk of permanent neurological sequelae. Two paralleled multicentre trials in the USA, reported together, have shown that 6 months of oral acyclovir after initial parenteral treatment may be beneficial.

The two trials together included 74 neonates with HSV infection, 29 with superficial disease, and 45 with CNS involvement. They were treated with parenteral acyclovir for 14 days (superficial disease) or 21 days (CNS disease). Randomisation was then to oral acyclovir or placebo three times daily for 6 months. Acyclovir suppressive therapy prolonged the time to two cutaneous recurrences in the CNS disease group but not in the superficial disease group. Among the 45 infants with initial CNS disease three had a CNS recurrence within 12 months of entering the study, one assigned to acyclovir and two to placebo. On the Mental Development Index of the Bayley Scales of Infant Development, performed at 12 months of age on 28 of the 45 infants, the mean score was significantly lower in the placebo group (68.12) than in the acyclovir group (88.24). There was a trend towards more neutropenia in the acyclovir group.

Six months of oral suppressive therapy with acyclovir after initial parenteral therapy may improve neurodevelopmental outcomes after neonatal HSV infection. An editorialist favours treating all children, with either superficial or CNS disease.

Kimberlin DW et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. *NEJM* 2011; 365: 1284-92; Gershon AA. Neonatal herpes simplex infection and the three musketeers. Ibid: 1338-9 (editorial)

Africa HEALTH CPD Challenge
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