

General

Global mortality patterns in young people

Almost a third of the world's population is in the 10–24 years age group yet there has been no detailed study of mortality in this group. Now such a study has been reported.

Data were derived from the 2004 *Global Burden of Disease Study*, national registry data, and revised all-cause mortality estimates developed for the 2006 *World Health Report*. In 2004 there were 2.6 million deaths of people aged 10–24 years. Of these deaths, 2.56 million (97%) were in low- and middle-income countries and 1.67 million (64%) were in sub-Saharan Africa and south-east Asia.

Mortality in this age group in low- or middle-income countries was 3.6 times that in high-income countries. At ages 10–14, 15–19, and 20–24 mortality was 16, 49, and 69 per 100 000 in high-income countries and 103, 150, and 244 per 100 000 in middle- and low-income countries. In Africa and south-east Asia, mortality was greater in females: in all other regions male mortality was higher than female. Maternal conditions accounted for 15% of female mortality. The largest cause of death was traffic accidents (14% of male deaths and 5% of female deaths). Violence caused 12% of male deaths and suicide was the cause of 6% of all deaths. HIV/AIDS and tuberculosis caused 11% of deaths.

Drowning caused 7%, 5%, and 2% of deaths at ages 10–14, 15–19, and 20–24.

Trauma needs to be added to HIV/AIDS and maternal conditions as priorities for global adolescent health policy. The *Lancet* commentator asserts that at least 75% of deaths in the second decade of life are preventable with established strategies.

Patton GC et al. Global patterns of mortality in young people: a systematic analysis of population health data. *Lancet* 2009; 374: 881–92; Blum RW. Young people: not as healthy as they seem. *Ibid*: 853–4.

Liraglutide for obesity

Liraglutide is glucagon-like peptide-1 (GLP-1) analogue similar in structure to human GLP-1, a gut-derived hormone. It induces weight loss, probably through actions on the brain and the gut, decreasing appetite and slowing stomach emptying. Now an international European trial has shown its effectiveness in the treatment of obesity.

A total of 564 adults (BMI 30–40 kg/m²) were randomised at 19 centres to one of six options: s.c. liraglutide daily at doses of 1.2, 1.8, 2.4, or 3.0 mg, s.c. placebo, or oral orlistat (a gastrointestinal lipase inhibitor) 120 mg three times daily, all for 20 weeks.

Mean weight loss with successively higher doses of liraglutide was 4.8, 5.5, 6.3, and 7.2 kg, with placebo 2.8 kg, and with orlistat 4.1 kg, a significant difference between liraglutide and either placebo or orlistat for all but the smallest dose of liraglutide. The proportion of subjects losing >5% of body weight was 29.6% with placebo, 44.2% with orlistat and 52.1%, 53.3%, 60.8%, and 76.1% with increasing doses of liraglutide. The corresponding figures for >10% weight loss were 2.0%, 9.5%, 7.4%, 18.9%, 22.8%, and 28.3%. Liraglutide reduced the prevalence of prediabetes by 84–96% at doses above 1.2 mg and also reduced blood pressure.

Liraglutide 3.0 mg daily improved measures of quality of life. Nausea and vomiting occurred more often with liraglutide but did not usually lead to cessation of treatment. Liraglutide was effective and well tolerated.

Astrup A et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 2009; 374: 1606–16; Bray GA. Gastrointestinal hormones and weight management. *Ibid*: 1570–1 (comment).

Tropical

House screening to prevent malaria in The Gambia

Making houses mosquito-proof by screening off access points should protect against malaria. In The Gambia it should be particularly effective because the primary vector, *Anopheles gambiae* sensu lato bites mainly indoors and at night. Now a trial in a Gambian town has shown the effectiveness of house screening.

A total of 500 houses in a town with low use of insecticide-treated bednets were randomised (2:2:1) to full screening (doors, windows, and closed eaves), screening ceilings only, or no screening (controls), and 462 houses were included in the final analysis. The mean number of *A gambiae* caught in traps was 37.5 per trap per night (controls), 15.2 (full screening) and 19.1 (ceiling screening), highly significant reductions of 59% and 47% with full and ceiling screening compared with controls. The

prevalence of anaemia (haemoglobin <80 g/L) among children aged 6 months to 10 years at the end of the transmission season was 19% in control houses and 12% in both full-screening and ceiling-screening houses, significant reductions in each case. Screening did not affect the frequency of parasitaemia.

House screening reduced the number of mosquitoes in the houses and lowered the prevalence of anaemia in children.

Kirby MJ et al. Effect of two different house-screening interventions on exposure to malaria vectors and on anaemia in children in The Gambia: a randomised controlled trial. *Lancet* 2009; 374: 998–1009; Gimnig JE, Slutsker L. House screening for malaria control. *Ibid*: 954–5 (comment).

Doxycycline for *Mansonella perstans* infection

Mansonella perstans is a filarial parasite endemic in central and western Africa. The larvae are transmitted via the bite of a midge (culicoides species) and microfilariae spread through the circulation and develop into adult worms in serous cavities, mesentery, and retroperitoneal tissues. Most infections are asymptomatic but symptoms may include angioedema, itching, fever, headache, arthralgia, serositis, and neurological disorders. Because of the frequency of coinfection with other filariae the cause of symptoms may be difficult to establish. Drugs such as diethylcarbamazine, ivermectin, and albendazole are not very effective against *M perstans*. This parasite has been shown to harbour the intracellular endosymbiont, wolbachia and filariae that do this respond to treatment with doxycycline.

[Wolbachia may be responsible for essential metabolic pathways in the worms.] Now a study in Mali has confirmed the effectiveness of doxycycline against *M perstans*.

A total of 216 patients with *M perstans* microfilaraemia were identified by screening of volunteers and randomised to doxycycline 200 mg daily for 6 weeks or no treatment. After 6 months subjects coinfecting with *Wuchereria bancrofti* were randomised to a single dose of albendazole and ivermectin or no treatment. *M perstans* microfilariae were undetectable in blood at 12 months in 67/69 subjects (97%) in the doxycycline group and 10/63 (16%) in the control group. At 36 months *M perstans* microfilariae suppression persisted in 75% of subjects treated with doxycycline only. Vomiting occurred in 17% (doxycycline) vs 4% (controls).

Doxycycline is an effective treatment for *M perstans* infection.

Coulibaly YI et al. A randomized trial of doxycycline for *Mansonella perstans* infection. *NEJM* 2009; 361: 1448–58; Hoerauf A. *Mansonella perstans* - the importance of an endosymbiont. *Ibid*: 1502–4 (editorial).

Bacteraemia in Kenyan children with sickle-cell anaemia

More than 80% of all children with sickle cell disease are born in Africa. There, more than 90% of children with the disease die before the diagnosis is made. Bacterial infection is a major cause of morbidity and mortality in sickle-cell disease and in the USA the main infecting organisms are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and non-typhi *Salmonella* species. In developed countries penicillin prophylaxis and vaccination with conjugate vaccines against *S pneumoniae* and *H Influenzae* type b have done much to improve prognosis but the main infecting organisms in African children with sickle-cell disease have been uncertain. Now a study in Kenya has shown that they are, in fact, similar to those in the USA.

Kilifi District Hospital on the coast of Kenya serves a population of around 500 000 people. About 88% of children are fully vaccinated against diphtheria, tetanus, and pertusis, *H influenzae* type B, and hepatitis B, but pneumococcal conjugate vaccine has not yet been introduced. The rate of HIV-positivity in antenatal clinics is 5–7%.

Between August 1998 and March 2008 a case-control study included 2157 children (<14 years old) admitted with bacteraemia (cases) and 13 492 controls. Overall, 6% of children admitted to hospital had bacteraemia (all had blood cultures). The prevalence of sickle-cell disease was 6% among cases and 1% among controls. The most common organisms isolated from children with sickle-cell disease were *S pneumoniae* (41% of isolates), non-typhi *Salmonella* species (18%), *H influenzae* type b (12%), *Acinetobacter* species (7%), and *Escherichia coli* (7%). After adjustment for age, children with sickle-cell disease were 26 times as likely as other children to have bacteraemia.

Children in Africa with sickle-cell disease are prone to infection with the same organisms as children with this disease in developed countries. Widespread use of pneumococcal and *H influenzae* type b conjugate vaccines is important for these children. *Lancet* commentators call for the introduction of haemoglobinopathy screening throughout Africa.

Williams TN et al. Bacteraemia in Kenyan children

with sickle-cell anaemia: a retrospective cohort and case-control study. *Lancet* 2009; 374: 1364–70; Hanks J, Ware RE. Sickle cell disease: an ounce of prevention, a pound of cure. *Ibid*: 1308–10 (comment).

Intermittent preventive treatment for malaria in infants

Sulfadoxine-pyrimethamine has been used successfully as intermittent preventive treatment against malaria for infants (IPTi) in Africa but there is concern about the development of drug resistance. It is argued that IPTi with a long-acting preparation will be necessary if prevention of infection is the aim whereas a short-acting preparation would be adequate if the aim is treatment of malarial infection.

Researchers at two sites in Tanzania, both with high rates of resistance to sulfadoxinepyrimethamine and one with moderate and one with low intensity of malaria transmission, have conducted a four-way randomised trial.

A total of 2419 infants were randomised to one of four options to be administered at the times of routine vaccinations at 2 months, 3 months, and 9 months of age. The options were sulfadoxine-pyrimethamine, chlorproguanil-dapsone (short-acting), mefloquine (long-acting), and placebo. At the low transmission site no treatment was effective. At the moderate-transmission site mefloquine had a protective efficacy of 38% against clinical malaria in infants aged 2–11 months but neither sulfadoxinepyrimethamine nor chlorproguanil-dapsone were significantly protective. None of the treatments protected against anaemia or hospital admission. Vomiting occurred after 8% of doses of mefloquine given on day 1. There were more deaths in the chlorproguanil-dapsone and mefloquine groups than in either of the other two groups.

Mefloquine protected against clinical malaria in the moderate-transmission area but sulfadoxine-pyrimethamine was not effective in these areas of very high resistance to this combination. These researchers conclude, however, that mefloquine is too poorly tolerated and new long-acting, safe drugs are needed.

A pooled analysis published next to the above trial includes six randomised, placebocontrolled trials, three in Ghana, and one each in Tanzania, Mozambique, and Gabon, of IPTi with sulfadoxine-pyrimethamine, given at times of routine vaccinations. The trials were conducted between 1999 and 2005 and the analysis included a total of 7930 infants. The protective efficacy of IPTi was 30% against

clinical malaria, 21% against anaemia, 38% against hospital admission with material parasitaemia, and 23% against hospital admission from any cause. Mortality was similar in IPTi and placebo groups.

WHO still recommends IPT with sulfadoxine-pyrimethamine but a *Lancet* commentator calls it 'a close call'. New drugs are being evaluated.

Gosling RD et al. Protective efficacy and safety of three antimalarial regimens for intermittent preventive treatment for malaria in infants: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 374: 1521–32; Aponte JJ et al. Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials. *Ibid*: 1533–42; McGready R. Intermittent preventive treatment of malaria in infancy. *Ibid*: 1478–80 (comment).

Diabetes

Treatment of mild gestational diabetes

Gestational diabetes mellitus (GDM) is associated with increased risk of subsequent established diabetes. There is less information about its effect on pregnancy outcomes. Severe GDM is associated with increased risk of fetal macrosomia and perinatal complications unless treated but the benefits of treating milder GDM are less clear. Now multicentre US study has shown the benefits of treating mild GDM.

A total of 958 women with mild GDM (abnormal glucose tolerance test result but fasting blood glucose <5.3 mmol/L) at 24–31 weeks gestation were randomised to treatment (diet, blood glucose self-monitoring, and insulin if necessary) or control (usual care) groups. The rate of the primary composite outcome (still-birth or perinatal death, or neonatal complications including hyperbilirubinaemia, hypoglycaemia, hyperinsulinaemia, or birth trauma) was similar in the two groups (32.4% in the treatment group and 37.0% in the control group). There were no perinatal deaths. Mean birth weight was 3302 vs 3408g, neonatal fat mass 427 vs 464g, and large-for-gestational age rate 7.1% vs 14.5%. A birth weight >4000g was recorded in 5.9% vs 14.3% and shoulder dystocia in 1.5% vs 4.0%. Caesarean section was performed in 26.9% vs 33.8%. Pre-eclampsia or gestational hypertension occurred in 8.6% vs 13.6%. Treatment of mild GDM reduced mean birth weight and the risks of macrosomia, shoulder

dystonia, caesarean section, and pre-eclampsia or gestational hypertension.

Landon MB et al. A multicentre, randomized trial of treatment for mild gestational diabetes. *NEJM* 2009; 361: 1339–48; Sacks DA. Gestational diabetes – whom do we treat? *Ibid*: 1396–8 (editorial).

Insulin treatment in type 2 diabetes

Patients with type 2 diabetes may have inadequate glucose control with oral drugs and may need insulin. The type of insulin required is, however, uncertain. Now the 3-year results of a multicentre trial in the UK and Ireland have been reported.

The trial included 708 patients who had unsatisfactory glycated haemoglobin levels on metformin and sulphonylurea treatment. Randomisation was to one of three insulin regimens: biphasic insulin aspart twice daily, prandial insulin aspart three times daily, or basal insulin detemir once daily (twice if necessary). Median glycated haemoglobin levels were similar in the three groups (biphasic 7.1%, prandial 6.8%, basal 6.9%). A level of 6.5% or less was achieved by 31.9%, 44.7%, and 43.2% respectively, significantly fewer in the biphasic group than in the other two groups. A second type of insulin was needed by 67.7%, 81.6%, and 73.6%. Mean yearly rates of hypoglycaemia were 3.0, 5.7, and 1.7 in the three groups respectively. Weight gain was greater in the prandial insulin group.

Basal or prandial insulin added to oral therapy gave better glycated haemoglobin levels and basal insulin was associated with less risk of hypoglycaemia and weight gain.

Holman RR et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *NEJM* 2009; 361: 1736–47; Roden M. Optimal insulin treatment in type 2 diabetes. *Ibid*: 1801–3 (editorial).

AIDS

Interleukin-2 added to anti-retrovirals: no benefit

Interleukin-2 increases levels of CD4+ cells by increasing CD4+ T-cell survival in patients treated with antiretroviral drugs for HIV infection. It is not known whether this provides clinical benefit. Now two international studies have shown no clinical benefit.

In the two studies HIV-infected patients with CD4+ cell counts of either 50–299 (SILCAAT study) or at least 300 CD4+ cells per cu. mm. (ESPRIT study) were randomised to interleukin-2 plus

antiretroviral therapy or antiretroviral therapy alone.

The SILCAAT study included 1695 patients with a median CD4+ cell count of 202 cells per cu. mm. and in the ESPRIT study there were 4111 patients with a median CD4+ cell count of 457 cells per cu. mm. Over an average follow up of 7–8 years CD4 counts were higher in the interleukin-2 groups, by 53 and 159 cells per cu. mm. on average in the SILCAAT and ESPRIT studies respectively. There were no significant differences between the interleukin-2 group and the control group in either study as regards risk of opportunistic disease, all-cause mortality, or grade 4 clinical events.

Adding interleukin-2 to antiretroviral therapy increased CD4+ cell counts but did not improve clinical outcomes.

The INSIGHT-ESPRIT study group and SILCAAT scientific committee. Interleukin-2 therapy in Patients with HIV infection. *NEJM* 2009; 361: 1548–59.

Paediatrics

Strict blood pressure control to slow progression of renal failure in children

In the treatment of adults with chronic kidney disease control of blood pressure is important and inhibitors of the renin-angiotensin system are the favoured drugs.

Children constitute <1% of people with chronic kidney disease but 50% of children with such disease are hypertensive. The benefits of strict blood pressure control in children with chronic kidney disease have been demonstrated in an international trial.

A total of 385 children with chronic kidney disease were randomised to intensive blood pressure control (target mean arterial pressure <50th percentile) or conventional control (target mean arterial pressure 50th–95th percentile). They were all treated with ramipril, 6 mg/sqm body surface area/day and non-renin-angiotensin-targeting drugs were added as necessary to achieve blood pressure control. Over an average follow-up of 5 years progression of kidney disease (end-stage renal failure or 50% or greater decline in renal function) occurred in 30% (intensive control) vs 42% (conventional control), a significant 35% risk reduction in the intensive control group. Adverse events were similar in the two groups.

Better blood pressure control delayed progression of kidney disease in children.

The ESCAPE trial group. Strict blood-pressure control and progression of renal failure in children. *NEJM* 2009; 361: 1639–50; Ingelfinger JR. Blood-pressure control and delay in progression of kidney disease in children. *Ibid*: 1701–3 (editorial).

Rotavirus vaccination in India: impact and cost-effectiveness

The WHO has recommended rotavirus vaccination in both developed and developing countries although the new vaccines are relatively expensive. Mathematical models have been used to estimate the public health impact and cost-effectiveness of mass vaccination with an oral live attenuated human rotavirus vaccine (RIX4414). Published clinical, epidemiological, and economic data were used, where possible using Indian data.

Without vaccination all children would have had at least one rotavirus infection by the age of 5 years and 94% would have had three such infections. With a national 35 million births a year mass infant vaccination would prevent 1745 000 severe episodes of gastroenteritis, 1794 500 outpatient visits, 203 000 admissions to hospital, and 41 000 deaths of children under the age of 5 years. The cost of vaccination was 8023 rupees (about £100 or US\$165) per life-year saved (less than India's per capita gross domestic product). The net programme cost would be equivalent to 11.6% of the 2006–2007 national healthcare budget. Vaccination would be cost-effective with a 94.7% probability using the criterion of cost of one life-year saved equal to per capita gross domestic product and a 97.8% probability with one life-year saved costing three times per capita gross domestic product.

Mass rotavirus vaccination of infants in India would take up almost 12% of the annual healthcare budget but it would prevent much morbidity and mortality with a cost-effectiveness within WHO criteria.

Rose J et al. Public health impact and cost effectiveness of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in India: model based analysis. *BMJ* 2009; 339: 787–91; Griffiths UK. Introduction of rotavirus vaccine. *Ibid*: 760–1 (editorial).

Infection

Seasonal trivalent inactivated vaccine protects against pandemic influenza A/H1N1 in Mexico

By the first week of July 2009 a total of 94 512 confirmed cases of pandemic

influenza A/H1N1 had been reported from 122 countries. The pandemic probably began in Mexico and southern California. Because the new virus contains a mixture of swine, avian, and human influenza genetic sequences it has been thought that seasonal vaccines would confer little or no protection against it. Now, however, data from Mexico have shown that the 2008–2009 trivalent inactivated vaccine did provide protection against influenza A/H1N1.

The frequency matched case-control study at a speciality hospital in Mexico City in March–May 2009 included 60 patients with laboratory-confirmed influenza A/H1N1 and 180 controls with other illnesses. Having received the trivalent inactivated vaccine (virus strains A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigen) provided 73% protection against influenza A/H1N1. Among cases, none of the eight who had received the vaccine died whereas 18/52 unvaccinated cases died. The proportions needing mechanical ventilation were 13% (vaccinated) vs 48% (unvaccinated).

The seasonal vaccine protected against pandemic influenza A/H1N1, especially against severe disease.

Garcia-Garcia L et al. Partial protection of seasonal trivalent inactivated vaccine against novel pandemic influenza A/H1N1 2009: case-control study in Mexico City. *BMJ* 2009; 339: 847 (pico), (b 3928); de Jong MD, Sanders RW. The future of influenza vaccines. *Ibid*: 815–6 (b4014) (editorial).

Cardiology

Cardiovascular risk factors: 38-year follow-up

The Whitehall study began in 1967–1970 and included 19019 male civil servants in London who were aged 40–69 at baseline. Now a 38-year follow-up has been reported, including 18863 men.

On entry to the study 42% of participants were current smokers, 39% had high blood pressure (systolic 140 mmHg or greater), and 51% had a high serum cholesterol (5 mmol/L or greater). Many of the smokers quit smoking shortly after study entry.

Life expectancy at age 50 was 23.7 years in men with all three of these risk factors at entry and 33.3 years in men with none of these risk factors. Men in the highest 5% for risk based on smoking, diabetes, employment grade, blood pressure, cholesterol, and BMI had a life

expectancy at age 50 of 20.2 years compared with 35.4 years for men in the lowest 5% for risk.

Risk factors in middle age were associated with considerable changes in life expectancy.

Clarke R et al. Life expectancy in relation to cardiovascular risk factors: 38 year follow-up of 19000 men in the Whitehall study. *BMJ* 2009; 339: 848 (pico), (b3513).

Migraine and cardiovascular disease

Migraine is associated with increased risk of ischaemic stroke. A systematic review and meta-analysis has provided further information.

The analysis included 25 published studies. Overall, from nine studies, the risk of ischaemic stroke was increased by 73% among people with migraine. Further analysis showed that the increased risk was confined to people with migraine with aura, who had a 2.2-fold increase whereas people with migraine without aura had a nonsignificant 23% increase. The risk in women was double that in men. Other factors associated with increased risk were young age (<45 years), smoking, and use of oral contraceptives. Migraine was not associated with increased risk of myocardial infarction or death from cardiovascular disease. There were insufficient data to assess the effect of aura or no aura on risks other than ischaemic stroke.

Migraine with aura is associated with increased risk of ischaemic stroke. Migraine in general does not increase the risks of myocardial infarction or death from cardiovascular disease.

Schürks M et al. Migraine and cardiovascular disease: systematic review and metaanalysis. *BMJ* 2009; 339: 1015 (pico) B3914; Loder E. Migraine with aura and increased risk of ischaemic stroke. *Ibid*: 981–2 (editorial).

Selective endothelin-receptor antagonist for treatment-resistant hypertension

Hypertension usually responds to treatment with one or two antihypertensive drugs. A few patients have treatment-resistant hypertension (unresponsive to the use of at least three drugs, including a diuretic, at full dosage). Serum levels of endothelin 1 are raised in patients with hypertension and diabetes and treatment with a non-selective endothelin-receptor antagonist (bosentan) has been shown to be effective in hypertension. Darusentan is a selective endothelin type A receptor antagonist. Now an international trial has shown that darusentan may be effective

for the treatment of previously drug-resistant hypertension.

A total of 379 patients were randomised at 117 centres in North and South America, Europe, New Zealand and Australia to additional treatment with darusentan at doses of 50, 100, or 300 mg daily, or placebo, for 14 weeks. The mean reductions in systolic/diastolic blood pressures were 17/10 mmHg (darusentan 50 mg), 18/10 mmHg (100 mg), 18/11 mmHg (300 mg), and 9/5 mmHg (placebo); highly significant reductions at all three doses compared with placebo. Oedema or fluid retention occurred in 27% (darusentan) vs 14% (placebo). Five patients on darusentan had serious cardiac adverse events: two with non-ST segment elevation myocardial infarction, two with fluid retention and heart failure, and one with atrial fibrillation and heart failure.

Darusentan might prove useful in the treatment of drug-resistant hypertension. Attention to diuretic therapy and fluid management would be needed.

Weber MA et al. A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 374: 1423–31; Williams B. Resistant hypertension: an unmet treatment need. *Ibid*: 1396–8 (comment).

Oncology

Early symptoms of ovarian cancer

Overall 5-year survival in ovarian cancer is about 35% but with early cancer 5-year survival is 80–90%. Only 30% of patients, however, are diagnosed in the early stages. Researchers in Devon, England have assessed early symptoms in an attempt to promote earlier diagnosis in general practice.

The study, in 39 general practices, included 212 women aged over 40 with ovarian cancer and 1060 age- and general practice-matched controls. On multivariable analysis, seven symptoms were associated with ovarian cancer: abdominal distension, postmenopausal bleeding, loss of appetite, increased urinary frequency, abdominal pain, rectal bleeding, and abdominal bloating. The positive predictive values were 2.5% (abdominal distension), 0.5% postmenopausal bleeding, 0.6% (loss of appetite), 0.2% urinary frequency, 0.3% (abdominal pain), 0.2% (rectal bleeding), and 0.3% (abdominal bloating). The odds ratios were 240, 24, 17, 16, 12, 7.6, and 5.3 respectively. At

least one of these symptoms was presented by 85% of cases and 15% of controls. Among symptoms presenting >180 days before diagnosis abdominal distension, urinary frequency, and abdominal pain were significant.

Attention to early symptoms, especially abdominal distension, might lead to earlier diagnosis of ovarian cancer.

Hamilton W et al. Risk of ovarian cancer in women with symptoms in primary care: population based case-control study. *BMJ* 2009; 339: 616 (pico); Fox

High-intensity exercise for cancer patients

Chemotherapy often induces intense fatigue in cancer patients. Studies have suggested that exercise training might reduce fatigue. Now researchers in Denmark have shown that high-intensity exercise training may be beneficial.

The study included 196 women and 73 men with 21 different kinds of cancer. Patients with brain or bone metastases were excluded. Randomisation was to conventional care plus exercise or conventional care alone. The exercise training consisted of high intensity physical training, relaxation training, body awareness training, and massage and took up 9 hours a week for 6 weeks. The intervention group did significantly better at 6 weeks on measures of fatigue, vitality, physical functioning, physical, emotional, and mental health, physical capacity, and muscular strength. There were no significant effects on global health status or quality of life.

The intervention reduced fatigue and improved measures of physical and emotional health but not quality of life.

Adamsen L et al. Effect of multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. *BMJ* 2009; 339: 895-9.

Neurology

Glatiramer acetate for early multiple sclerosis

Glatiramer acetate is approved for the treatment of relapsing-remitting multiple sclerosis (MS). Patients who present with neurological episodes that are probably due to demyelination but do not have the lesions spread in space and time needed for a diagnosis of MS are said to have clinically isolated syndrome (CIS). Now an international trial has shown that glatiramer acetate delays the onset of clinically

definite MS in patients with CIS.

A total of 481 patients with CIS (unifocal disease, at least two T2-weighted brain lesions of 6 mm or larger) were randomised at 80 centres in 16 countries to s.c. glatiramer acetate 20mg daily, or placebo for up to 36 months. A second attack occurred in 24.7% (glatiramer acetate) vs 42.9% (placebo) a highly significant 59% reduction in the treatment group. The risk of conversion to clinically definite MS was reduced by 45% in the treatment group compared with the placebo group, also highly significant. The time taken for 25% of patients to convert to clinically definite MS was 722 days vs 336 days. The number-needed-to-treat to prevent one conversion was 5.5. Injection-site reactions (56% vs 24%) and immediate post-injection reactions (19% vs 5%) were more frequent in the treated group. The number of new T2 lesions was reduced by 58% in the treated group compared with the control group.

Early treatment with glatiramer acetate delays conversion from CIS to clinically definite MS. Against this is to be balanced the fact that less than half of the placebo group converted.

Comi G et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): a randomised, double-blind, placebo-controlled study. *Lancet* 2009; 374: 1503-11; Miller DH, Leary SM. Treatment of clinically isolated syndrome: to be pre-CISe. Ibid: 1475-6. (comment).

Rasagiline for Parkinson's disease: disease-modifying or not?

Rasagiline is an inhibitor of monoamine oxidase type B (MAO-B) approved for the symptomatic treatment of Parkinson's disease. Laboratory models have suggested that it may also have a neuroprotective effect and could be potentially disease modifying in Parkinson's disease. This possibility has been investigated in a multinational trial.

The trial was of the delayed-start design aimed at detecting a disease-modifying effect. In the first 36-week phase randomisation was to rasagiline 1mg daily, rasagiline 2mg daily, or placebo (1:1:2). In the second 36-week phase treatment continued as before in the first two groups and the placebo group were rerandomised to rasagiline 1mg or 2mg daily. In the groups receiving 1mg daily of rasagiline the early treatment group did better throughout the 72 weeks, suggesting a possible disease-modifying effect. There was no such effect in the 2mg daily groups. The question of whether or

not rasagiline has a disease-modifying effect remains unanswered.

Olanow CW et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *NEJM* 2009; 361: 1268-78; D'Agostino RB. The delayed-start study design. Ibid: 1304-6 (Statistics in medicine).

Carpal tunnel syndrome: surgery vs non-surgical therapy

Current evidence suggests that surgery is better than non-surgical treatments for patients with carpal tunnel syndrome but the evidence is incomplete. Now researchers in Washington state and New Hampshire have shown better results with surgery compared with multimodal non-surgical therapy although the advantage was only modest.

A total of 116 patients with carpal tunnel syndrome without denervation were randomised to surgery (open or endoscopic decompression) or non-surgical therapy (ibuprofen plus 'hand therapy', including hand exercises, ligament stretching, tendon gliding, splinting, and ultrasound). At 12 months outcomes as regards function and symptoms were significantly better in the surgery group. There were no complications of surgery.

Surgery provided a significant but modest advantage over non-surgical therapy. However, 61% of patients in the non-surgical group were able to avoid surgery.

Jarvik JG et al. Surgery versus non-surgical therapy for carpal tunnel syndrome: a randomised parallel-group trial. *Lancet* 2009; 374: 1074-81; The Lancet. Surgical research: the reality and the IDEAL. Ibid: 1037 (editorial); Atroshi I, Gummesson C. Non-surgical treatment in carpal tunnel syndrome. Ibid: 1042-4.

Obs & Gyn

Improved community-based drug provision to prevent maternal deaths in Africa: mathematical model

Over the last two decades there has been little improvement in maternal mortality rates in sub-Saharan Africa: maternal mortality ratio was 921 per 100 000 live births in 1990 and 905 per 100 000 live births in 2005. A mathematical model was developed using published data about maternal deaths from post-partum haemorrhage (PPH) or sepsis. Three possible intervention packages were considered for Malawi and for sub-Saharan Africa as a whole: 1) strengthening of health facilities, 2) health facility strengthening plus improved drug provision via ante-

natal-care appointments and community health workers, and 3) option 2 plus improved community-based drug provision via female volunteers in villages.

The lowest risk deliveries were in health facilities. In Malawi (2860 maternal deaths per year from PPH or sepsis) it was estimated that packages 1, 2, and 3 would prevent 7%, 25%, and 36% of these deaths. For sub-Saharan Africa (182 000 deaths) the estimated reductions were 12%, 24%, and 32% respectively. The effects were greatest for the poorest women.

Community-based drug provision (misoprostol and antibiotics) could significantly reduce maternal deaths from PPH and postpartum sepsis in sub-Saharan Africa.

Page C et al. Estimation of potential effects of improved community-based drug provision, to augment health-facility strengthening, on maternal mortality due to postpartum haemorrhage and sepsis in sub-Saharan Africa: an equity-effectiveness model. *Lancet* 2009; 374: 1441–8; Horton R. What will it take to stop maternal deaths? *Ibid*: 1400–2 (comment).

Labour induction for gestational hypertension or mild pre-eclampsia

Hypertensive disorders in pregnancy are a major cause of maternal and neonatal morbidity and mortality globally. Most such disorders present late in pregnancy. Induction of labour may prevent eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet count), placental abruption, maternal death, and neonatal asphyxia. On the other hand it may increase the risk of instrumental delivery or caesarean section. Now a trial in The Netherlands has shown that induction of labour beyond 37 weeks gestation improves outcomes for women with gestational hypertension or mild pre-eclampsia.

The trial, at 38 centres, included 756 women with gestational hypertension or mild pre-eclampsia in a singleton pregnancy at 36–41 weeks. Randomisation was to induction of labour or expectant monitoring. A poor maternal outcome (death, eclampsia, HELLP syndrome, pulmonary oedema, thromboembolism, placental abruption, severe hypertension or proteinuria, or major post-partum haemorrhage) occurred in 31% (induction of labour) vs 44% (expectant monitoring), a highly significant 29% reduction with induction. No patient died or developed eclampsia and there were no neonatal deaths.

These researchers advise induction of labour for women with mild hyperten-

sive disease beyond 37 weeks gestation.

Koopmans CM et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks gestation (HYPI-TAT); a multicentre, open-label randomised controlled trial. *Lancet* 2009; 374: 979–88; Johnson DD. Induced labour for pre-eclampsia and gestational hypertension. *Ibid*: 951–2 (comment).

HPV-16 oncoprotein vaccination for vulvar intraepithelial neoplasia

In more than three-quarters of cases, vulvar intraepithelial neoplasia (VIN) is associated with infection with human papillomavirus type 16 (HPV-16). The viral oncoproteins E6 and E7 are important in the development of VIN and progression to invasive cancer. Patients with grade 3 VIN are deficient in T cells that react against HPV-16 E6 and E7 oncoproteins. Now researchers in the Netherlands have assessed the use of vaccination against these proteins in the treatment of grade 3 VIN.

The vaccine was a synthetic long-peptide vaccine containing a mix of long peptides from the HPV-16 viral oncoproteins E6 and E7 in incomplete Freund's adjuvant.

Twenty women with HPV-16-positive grade 3 VIN received three or four doses at 3-week intervals. At 3 months after the last dose 12 women had had a clinical response, with complete regression of VIN in five. Four of these became HPV-16-negative. At 12 months 15 patients had had a clinical response and nine complete regression. The complete responses persisted at 24 months. All patients had vaccine-induced T cell responses. A complete response at 3 months was associated with stronger CD4+ and CD8+ T-cell responses. All 20 patients had local swelling at the injection site and 64% developed fever. Spontaneous regression of VIN occurs in <1.5% of patients.

Vaccination may induce cellular immunity and cause regression of VIN.

Kenter GG et al. Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. *NEJM* 2009; 361: 1838–47; Finn OJ, Edwards RP. Human papillomavirus vaccine for cancer prevention. *Ibid*: 1899–1901 (editorial).

Pulmonary

Non-invasive ventilation after extubation

The use of non-invasive (face-mask) ventilation after extubation in respiratory crises for patients with chronic respiratory

disorders may prevent reintubation and improve rates of survival. A multicentre trial in Spain has confirmed the benefit.

The trial included 106 intubated and mechanically ventilated patients with chronic respiratory disorders who were hypercapnic after a successful trial of spontaneous breathing. Randomisation was to noninvasive ventilation or conventional oxygen treatment after extubation. Respiratory failure ensued within 72 hours in 15% (non-invasive ventilation) vs 48% (controls), a highly significant difference.

Among 27 patients with respiratory failure not needing immediate reintubation, 17 were successfully treated with non-invasive ventilation. Mortality at 90 days was 11% (non-invasive ventilation) vs 31% (controls).

These researchers suggest that non-invasive ventilation after extubation should be routine in these circumstances.

Ferrer M et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet* 2009; 374: 1082–8; Calverley PMA. Leaving invasive ventilation behind. *Ibid*: 1044–5 (comment).

Gastrology

Soluble fibre for irritable bowel syndrome

Fibre, usually insoluble fibre (bran), is often used in the treatment of irritable bowel syndrome (IBS) but its effectiveness is uncertain. Until now, studies have taken place in hospitals and have had methodological limitations. Now a study in general practice in the Netherlands has compared insoluble and soluble fibre (psyllium).

A total of 275 patients aged 18–65 years with IBS were randomised to 12 weeks of treatment with psyllium, bran, or placebo (rice flour). In the first 2 months the proportion of responders was significantly greater with psyllium than with placebo. Only in the third month was bran better than placebo but the significance of this finding was questionable. After 3 months, symptom severity was reduced significantly in the psyllium group but not in the bran group. Some patients experienced worsening of symptoms on bran.

Psyllium gives better results than bran in the treatment of IBS in general practice. Bijkerk CJ et al. Soluble or insoluble fibre in irritable bowel syndrome in primary care? Randomised placebo controlled trial. *BMJ* 2009; 339: 613–5.