

General

Health financing in developing countries

There is great debate about the financing of health in developing countries, the roles of governments and non-governmental organisations (NGOs), and the effects of aid donations (developmental assistance for health, DAH). An analysis of available data has been reported.

The analysis included data from government reports in developing countries and from WHO and the International Monetary Fund (IMF). The aim was to measure government expenditures on health as agent (GHE-A) in developing countries (including domestically and externally financed expenditure) and to assess the association between government domestic spending on health, gross domestic product (GDP), government size, HIV prevalence, debt relief, and DAH to governmental and non-governmental sectors.

Overall, there was a doubling of public financing of health from domestic sources in developing countries between 1995 and 2006. There was an increase in GDPs with a slight reduction in the proportion of GDP spent by governments but an increase in the proportion of government spending going to health. The share of government spending on health, however, decreased in many countries in sub-Saharan Africa.

DAH to governments resulted in reduced domestic government spending on health so that for every US dollar of such DAH the governments would spend \$0.43 to \$1.14 less of their own money on health. On the other hand, DAH given to NGOs had a significant positive effect on domestic government health spending. Debt relief had no effect on domestic government health spending. These researchers recommend monitoring of government health expenditures, collaborative targets for government health spending, efforts to increase the effectiveness of DAH, assessment of the risks and benefits of DAH to NGOs, and looking into the use of global price subsidies or product transfers as forms of DAH. Lancet commentators cast doubt on the reliability of the data, warn against concluding that DAH should be aimed at NGOs and not at governments, and call for more research.

Lu C et al. Public financing of health in developing countries: a cross-national systematic analysis. *Lancet* 2010; 375: 1375–87; Sridhar D, Woods N. Are there

simple conclusions on how to channel health funding. Ibid: 1326–8; Ooms G et al. Crowding out: are relations between international health aid and government health funding too complex to be captured in averages only? Ibid: 1403–5 (viewpoint).

Worldwide mortality at ages 15–59

With the Millennium Development Goals attention has been focused on child mortality, maternal mortality, and mortality from specific diseases such as malaria, tuberculosis, and HIV infection. Relatively little attention has been paid to overall deaths in people aged 15–59 (premature adult deaths). Now data have been presented from 187 countries for such deaths (45q15) from 1970 to 2010.

A database was compiled of 3889 measurements of adult (age 15–59) mortality using data from registers, censuses, and surveys. The probability of death between the ages of 15 and 60 (45q15) was estimated for each year for men and women. The value of 45q15 (probability of death between age 15 and 59 per 1000 people) in 2010 varied from 65 for men in Iceland and 38 for women in Cyprus to 765 for men in Swaziland and 606 for women in Zambia. Worldwide 45q15 fell from around 260 in 1970 to around 210 in 2010 for men and from around 200 in 1970 to around 130 in 2010 for women. There were increases in the countries of the former Soviet Union (in Russia from 121 to 157 among women and from 308 to 412 among men between 1970 and 2010) and in sub-Saharan Africa (largely because of the AIDS epidemic). There was a considerable decrease in female 45q15 in south Asia. In large countries of southeast Asia there was a halt in the decline of 45q15.

Premature adult mortality varies around the world. Deaths at these ages deserve more attention.

Rajaratnam JK et al. Worldwide mortality in men and women aged 15–59 years from 1970 to 2010; a systematic analysis. *Lancet* 2010; 375: 1704–20; Koyanagi A, Shibuya K. What do we really know about adult mortality worldwide? Ibid: 1668–70. (comment).

Paediatrics

Trends in under-5s mortality 1970–2010

Although many countries look likely to fail to achieve Millennium Development Goal 4 (MDG4) there is, nevertheless, evidence of progress in reducing mortality in children <5 years old. Data from

187 countries have been used to assess trends between 1970 and 2010.

Global under-5s mortality fell from around 16 million deaths in 1970 to around 11.9 million in 1990 and an estimated 7.7 million for 2010. This 7.7 million will be made up of 3.1 million neonatal deaths, 2.3 million at age 1 month to 1 year, and another 2.3 million at ages 1–4 years. Less than 1% of these deaths occur in rich countries: about half of them are in sub-Saharan Africa and a third in south Asia. To reach MDG4 would need a yearly reduction of 4.4% but the current global reductions amount to just over 2% a year. The rate of reduction has, however, accelerated around the world with 13 regions (including all regions of sub-Saharan Africa) achieving greater rates of decline in under-5s mortality in the first decade of this century than in the 1990s.

Even though MDG4 may not be reached considerable progress is being made.

Rajaratnam JK et al. Neonatal, postneonatal, childhood, and under-5 mortality for 187 countries, 1970–2010: a systematic analysis of progress towards Millennium Development Goal 4. *Lancet* 2010; 375: 1988–2008; Horton R. The continuing invisibility of women and children. Ibid: 1941–3 (comment).

Non-financial incentives for childhood immunisations

Conditional cash transfer programmes improve the use of preventive health services. A study in rural India has shown that non-financial incentives may improve child immunisation rates.

In Rajasthan, India, a total of 134 villages in a low-income area with very low immunisation rates were randomised to three options: increased regular immunisation clinics, similar clinics with small incentives (1 kg of dried beans at each immunisation of children aged 1–3 years and a set of plates on completion), or control group. The rates of complete immunisation were 39% (extra clinics plus incentives), 18% (extra clinics, no incentives), and 6% (controls).

Compared with the control villages, extra clinics increase the rate of full immunisation three-fold, and extra clinics plus incentives increase it seven-fold. Among villages with extra clinics the provision of incentives doubled the rate of full immunisation. In poor rural villages with very low immunisation rates extra immunisation clinics improved take-up rates and small non-financial incentives produced further improvement. Banerjee AV et al. Improving immunisation coverage in rural India: clustered randomised controlled evaluation of immunisation campaigns with and without

incentives. *BMJ* 2010; 340: 1291 (e2220); Das J. Improving immunisation coverage in rural India. *Ibid*: 1257–8 (c2553) (editorial).

High-frequency oscillatory ventilation versus conventional ventilation for very preterm infants

Animal research has strongly suggested that high frequency oscillatory ventilation (HFOV) might reduce the risk of bronchopulmonary dysplasia among preterm infants needing ventilation for the respiratory distress syndrome. Trials in human infants, however, have given varying results and the comparative merits of HFOV and conventional ventilation are still debated. A systematic review and meta-analysis of individual patient data from 10 randomised controlled trials has been reported.

The ten trials included a total of 3229 preterm neonates. The relative risks of death or bronchopulmonary dysplasia at 36 weeks postmenstrual age, of death or severe neurological deficit, or of any of these individual outcomes were almost the same with HFOV or conventional ventilation. No subgroups of neonates who benefited more or less from HFOV could be identified. Further analysis might define such subgroups.

Cools F et al. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. *Lancet* 2010; 375: 2082–91; Parod RB. HFOV in preterms: an individual patients' data meta-analysis. *Ibid*: 2054–5 (comment).

Child mortality in 2008

Estimates of mortality in children <5 years old have been reported with data from 193 countries. These data are now published annually to assess progress towards Millennium Development Goal 4 (a two-thirds reduction in under-5s mortality between 1990 and 2015).

In 2008, there were 8.795 million deaths in this age group worldwide. Most of the deaths (68%) were due to infection, the three biggest killers being pneumonia, diarrhoea, and malaria, causing 18%, 15%, and 8% of the total number of deaths respectively. Neonatal mortality accounted for 41% of the total and the main causes of death in the neonatal period were complications of preterm birth, birth asphyxia, sepsis, and pneumonia. Other notable causes of under-5s mortality were congenital abnormalities (4.3% of the total), injuries (3.3%), AIDS (2.3%), pertussis (2.2%), and meningitis (1.9%). Five countries (India, Nigeria, Democratic Republic of

the Congo, Pakistan, and China) suffered almost half (49%) of the deaths. Most of the deaths from malaria or AIDS were in sub-Saharan Africa.

Black RE et al. Global, regional, and national causes of child mortality in 2008; a systematic analysis. *Lancet* 2010; 375: 1969–87; Horton R. The continuing invisibility of women and children. *Ibid*: 1941–3.

Tropical

Pyronaridine-artesunate vs artemether-lumefantrine for uncomplicated *Plasmodium falciparum* malaria in Africa and Asia.

Recommended first-line treatment for malaria is with artemether-lumefantrine but there are drawbacks: twice daily dosage, fatty diet needed for optimal absorption, and short half-life with risk of early reinfection. A fixed-dose (3:1) combination of pyronaridine and artesunate has given promising results in preliminary studies. Now a multinational phase 3 study has been reported.

At seven sites in Africa and three in southeast Asia a total of 1272 patients aged 3–60 years with uncomplicated *Plasmodium falciparum* malaria were randomised (2:1) to tablets of pyronaridine-artesunate (180 mg/60 mg) daily (P-A) or artemether-lumefantrine (20 mg/120 mg) twice daily (A-L), with dosage by body weight. The PCR-corrected adequate clinical and parasitological response (ACPR) rate at day 28 was 99.5% (P-A) vs 99.2% (A-L). The adverse event rates were 60% vs 57%.

Eosinophilia occurred in 6.2% vs 5.7% and 2.5% vs 1.7% were withdrawn from the study. Raised liver enzyme levels were more frequent with P-A. Pyronaridine-artesunate was non-inferior to artemether lumefantrine.

Tshefu AK et al. Efficacy and safety of a fixed-dose oral combination of pyronaridine-artesunate compared with artemether-lumefantrine in children and adults with uncomplicated *Plasmodium falciparum* malaria: a randomised non-inferiority trial. *Lancet* 2010; 375: 1457–67; Nosten FH. Pyronaridine-artesunate for uncomplicated falciparum malaria. *Ibid*: 1413–4 (comment).

New Ebola virus treatment tested in rhesus macaque monkeys

Small interfering RNAs (siRNAs) have been shown to inhibit the replication of hepatitis and severe acute respiratory syndrome (SARS) viruses in non-human primates. Case fatality rates of up to 90% have been reported for Zaire Ebola virus

(ZEBOV) infection. Now researchers in the USA have used siRNAs that targeted three different ZEBOV protein genes, all formulated in stable nucleic acid-lipid particles (SNALPs). Three monkeys were given the siRNAs i.v. at 30 minutes and on days 1, 3, and 5 after receiving a lethal i.m. dose of ZEBOV. Four others were given the siRNAs at 30 minutes and on days 1, 2, 3, 4, 5, and 6. Only one monkey (in the first group) died. All three animals in this (four-dose) group developed symptoms of haemorrhagic fever. In the seven-dose group all four animals survived and their symptoms were less severe. The treatment was well tolerated.

This study shows that RNA interference may be useful as postexposure treatment for Ebola virus infection.

Geisbert TW et al. Postexposure protection of non-human primates against lethal Ebola virus challenge with RNA interference: a proof-of-concept study. *Lancet* 2010; 375: 1896–905; Feldman H. Are we any closer to combating Ebola infections? *Ibid*: 1850–2 (comment).

WHO antibiotic guidelines for children in a very high malaria-transmission area: not effective

WHO guidelines for the use of antimicrobials have not been tested fully in areas of intense malaria transmission. In much of rural Africa there is uncertainty about antibiotic policy. Now a study in Tanzania in an area of very high malaria (*Plasmodium falciparum*) transmission has exposed defects in the WHO guidelines. The study included 3639 children aged 2 months to 13 years admitted to hospital with a febrile illness. The hospital served a rural population of around 277 000 people in an area with an under-5 mortality of 165 per 1000, *P falciparum* transmissions of 50–700 bites per person per year, and no routine immunisation against *Streptococcus pneumoniae* or *Haemophilus influenzae* type b. Of the 3639 children, 2195 (60%) had positive malaria slides, 341 had invasive bacterial disease (IBD), and 142 were HIV-positive. Mortality was 3.7% with parasitaemia alone, 14% with parasitaemia and IBD, 14% with parasitaemia and HIV, 18% with IBD alone, 26% with IBD and HIV, 8% with HIV alone, and none in four children with parasitaemia, IBD, and HIV. Among all children with IBD mortality was 17% and among all children without IBD it was 3.8%. The presence or absence of parasitaemia did not affect this difference. The WHO criteria were 67.4% sensitive for IBD and 51.5% specific. Slide positivity reduced IBD sensitivity from 70.5% to 60.0%

and increased specificity from 48.1% to 53.5%. The sensitivity decreased with increasing parasite density. The WHO criteria picked up IBD in 82.8% of IBD cases who died and in 64.3% of IBD cases who survived. Nevertheless using these criteria 10 of the 58 children who died of IBD would not have been treated with antimicrobials. Among children with WHO criteria for IBD less than half (47%) of the organisms isolated were sensitive to the first recommended antibiotic.

Current WHO criteria may fail to identify children with IBD and may recommend the wrong antibiotic. The criteria may fail to identify non-typhi *Salmonella* infections in particular for which malaria is probably a risk factor. The addition of severe anaemia and prostration to current indications would significantly improve detection of IBD. Ceftriaxone alone or ciprofloxacin plus penicillin might be better first choice treatment for IBD in severely ill children in malarious areas.

Nadjim B et al. WHO guidelines for antimicrobial treatment in children admitted to hospital in an area of intense *Plasmodium falciparum* transmission: prospective study. *BMJ* 2010; 340: 848 (c1350); Maitland K. Antimicrobials in children admitted to hospital in malaria endemic areas. *Ibid*: 822–3 (c1818).

Obs & Gyn

Global maternal mortality, 1980–2008

Maternal mortality includes death in pregnancy, during labour, or in the 42 days after delivery. Millennium Development Goal (MDG) 5 is a 75% reduction in maternal mortality between 1990 and 2015. Accurate data about maternal mortality in developing countries have been difficult to obtain but the methodology has improved in recent years. Now data from 181 countries for the years 1980 to 2008 have been reported.

Data were obtained from vital registration data, censuses, surveys, and verbal autopsy studies. Estimated global maternal mortality was 526 300 in 1980 and 342 900 in 2008. The global maternal mortality ratio (MMR, maternal deaths per 100 000 live births) was 422 in 1980, 320 in 1990, and 251 in 2008. The yearly rate of decline in MMR since 1990 was 1.3% overall, varying from a decline of 8.8%/year in the Maldives to an increase of 5.5%/year in Zimbabwe. In 2008, more than half of all maternal deaths were in six countries: India, Nigeria,

Pakistan, Afghanistan, Ethiopia, and the Democratic Republic of the Congo. Of the 342 900 maternal deaths in 2008 about 61 400 were due to HIV infection. Twenty-three countries are likely to achieve MDG5. Other countries such as Egypt, China, Ecuador, and Bolivia are making progress. Progress has been made in collecting data about maternal mortality. Although only a minority of countries are on track to achieve MDG5 others are making progress.

Hogan MC et al. Maternal mortality for 181 countries, 1980–2008: a systematic analysis of progress towards Millennium Development Goal 5. *Lancet* 2010; 375: 1609–23; Horton R. Maternal mortality: surprise, hope, and urgent action. *Ibid*: 1581–2.

Vitamin A to reduce maternal mortality: negative trial in Ghana

Vitamin A supplements reduce mortality in young children in developing countries and a trial in Nepal showed that they might also reduce maternal mortality. In a cluster-randomised trial in predominantly rural Ghana a total of 1086 residential clusters (207 781 women aged 15–45) were randomised by cluster of residence to weekly oral vitamin A, 25000 IU retinol equivalents, or placebo. In the vitamin A group the mortality rate was 348 deaths per 100 000 pregnancies or 453 deaths per 100 000 women-years. In the placebo group the rates were 377 deaths per 100 000 pregnancies or 449 deaths per 100 000 woman-years. Neither of these differences was significant.

In this trial vitamin A supplementation did not reduce maternal mortality. It is concluded that present evidence does not support vitamin A supplementation for women and further similar trials are unlikely to be undertaken because of their size and cost.

Kirkwood BR et al. Effect of vitamin A supplementation in women of reproductive age on maternal survival in Ghana (ObaapaVitA): a cluster-randomised, placebo-controlled trial. *Lancet* 2010; 375: 1640–9.

Misoprostol plus uterotonics for post-partum haemorrhage

There are about 125 000 deaths from postpartum haemorrhage (PPH) worldwide each year, most of them in developing countries. A trial in Argentina, Egypt, South Africa, Thailand, and Vietnam has not supported the use of misoprostol added to standard uterotonics for the treatment of PPH.

A total of 1422 women with PPH were randomised to uterotonics with or without sublingual misoprostol, 600 µg.

Blood loss of at least 500 ml within 60 minutes occurred in 14% of each group. Shivering and fever were more frequent in the misoprostol group.

The addition of misoprostol to standard uterotonics provided no benefit in the treatment of PPH. Misoprostol could be effective when used alone but WHO has advised against its community distribution and use. *Lancet* commentators question this advice and call for an emergency meeting of WHO and the International Federation of Gynecology and Obstetrics (FIGO) to discuss the community use of misoprostol. They write that Millennium Development Goal 5 is unlikely to be achieved in sub-Saharan Africa without the community use of misoprostol.

Nidmer M et al. Misoprostol as an adjunct to standard uterotonics for treatment of post-partum haemorrhage: a multicentre double-blind randomised trial. *Lancet* 2010; 375: 1808–13; Potts M et al. Maternal mortality: one death every 7 min. *Ibid*: 1762–3.

Umbilical cord blood pH and cerebral injury

A low pH in umbilical cord blood is commonly used as a measure of birth asphyxia but there is uncertainty about the association between low cord blood pH and neonatal morbidity and mortality. A systematic review and meta-analysis has confirmed the link.

The review included 51 studies and 490 625 neonates. A low umbilical cord arterial pH increased the risk of neonatal death by a factor of 4.2 in a high-risk population and by a factor of 16.9 in an unselected population. The risk of neonatal morbidity was increased by factors of 3.4 and 10.6 in these populations respectively. Low cord blood pH was specifically associated with hypoxic-ischaemic encephalopathy, seizures, intraventricular haemorrhage, and cerebral palsy. Low pH in umbilical arterial blood is associated with increased neonatal mortality and morbidity.

Malin GL et al. Strength of association between umbilical cord pH and perinatal and long-term outcomes: systematic review and meta-analysis. *BMJ* 2010; 340: 1121 (c1471); Neilson JP. Umbilical cord blood gas analysis. *Ibid*: 1092–3 (c1720).

Infection

Antibiotics and bacterial antibiotic resistance in individuals

A systematic review and meta-analysis has shown that after a course of antibiotics

individual patients are more likely to harbour bacteria resistant to the antibiotic used. The analysis included 24 studies. Exposure to an antibiotic within the last 2 months significantly increased the risk of isolation of resistant bacteria from the urine 2.5-fold and from the respiratory tract 2.4-fold. Exposure in the last 12 months was associated with increased risks of 1.3-fold and 2.4-fold respectively. The risk of isolating resistant bacteria increased with the number of antibiotic courses. The use of antibiotics increases the likelihood of carriage of resistant bacteria in the individual and the pool of resistant bacteria in the community.

Costelloe C et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; 340: 1120 (c2096); So AD et al. Tackling antibiotic resistance. *Ibid*: 1091–2 (c2071) (editorial).

Extensively drug-resistant tuberculosis in South Africa

Extensively drug-resistant (XDR) tuberculosis (resistant to at least rifampicin, isoniazid, a fluoroquinolone, and at least one second-line injectable drug such as amikacin, kanamycin, or capreomycin) has been reported from nine countries. Reports of treatment success rates have varied. In Peru, more than half of patients with XDR tuberculosis were cured or completed treatment. In KwaZulu Natal, South Africa, almost all patients with XDR tuberculosis had HIV infection and died. Now a retrospective cohort study from four provincial treatment facilities in South Africa has been reported.

The study included 195 patients with XDR tuberculosis between August 2002 and February 2008. Twenty-one of these patients died before treatment. Of the remaining 174 patients 82 (47%) had HIV infection and 62 (36%) died during follow-up. Mortality was not significantly different with or without HIV infection (41% vs 30%). Treatment with moxifloxacin and with multiple drugs were both significantly associated with reduced mortality and previous proved multidrug-resistant (MDR) tuberculosis was associated with a five-fold increase in mortality. Highly active antiretroviral therapy reduced mortality among patients with HIV infection. Mycobacterial cultures converted to negative in 33 patients (19%), within 6 months of starting antituberculosis treatment in 23.

More than half of the patients in this study did not have HIV infection. Survival among patients with HIV infection was better than previously reported.

National aims continue to be the prevention of XDR tuberculosis and early detection and treatment of XDR and MDR tuberculosis.

Dheda K et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet* 2010; 375: 1798–807; Das P, Horton R. Tuberculosis – time to accelerate progress. *Ibid*: 1755–7 (comment); Ghebreyesus TA et al. Tuberculosis and HIV – time for intensified response. *Ibid*: 1757–8 (comment); Miglion GB, Sotgin G. XDR tuberculosis in South Africa: old questions, new answers. *Ibid*: 1760–1 (comment); Lönnroth K et al. Tuberculosis control and elimination 2010–50: cure, care, and social development. *Ibid*: 1814–29 (Series, tuberculosis 1); Gandhi NR et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. *Ibid*: 1830–43 (Series, tuberculosis 2).

AIDS

Treatments to reduce mother-to-child HIV-1 transmission in Malawi

It is estimated that about 200 000 infants are infected with HIV-1 via breast milk each year and without treatment half of them will die within 2 years. Bottle feeding reduces the risk of HIV-1 infection but is itself associated with increased mortality. Triple antiretroviral (ART) therapy for the mother has been compared with nevirapine prophylaxis for the mother in a trial in Malawi.

The study included 2369 mother-infant pairs. All the mothers were HIV-1 positive with a CD4 cell count of at least 250 cells per cu.mm and were asked to breast feed exclusively for 24 weeks. All mothers took zidovudine/lamivudine twice daily from the onset of labour until 7 days after delivery and a single dose of nevirapine in labour. All infants were given a single dose of nevirapine soon after birth and twice daily zidovudine/lamivudine for 7 days. Randomisation was to maternal ART for 28 weeks, infant nevirapine for 28 weeks, or no continuing antiretrovirals (controls). The rate of infant HIV-1 positivity at age 2 weeks was 5%. The estimated risks of HIV-1 transmission at between 2 and 28 weeks were 2.9% (maternal ART), 1.7% (infant nevirapine), and 5.7% (controls). The estimated risks of infant HIV-1 infection or death between 2 and 28 weeks were 4.1%, 2.6%, and 7.0% respectively. The incidence of maternal neutropenia was 6.2%, 2.6%, and 2.3%. A hypersensitivity reaction occurred in 1.9% of infants given nevirapine. The protective efficacy against HIV-1 transmission at between 2 and 28 weeks was 74% for infant nevi-

rapine and 53% for maternal ART.

Both maternal ART and infant nevirapine were effective. The study was not powered to compare the two regimens.

Chasela CS et al. Maternal or infant antiretroviral drugs to reduce HIV-1 transmissions. *NEJM* 2010; 362: 2271–81; Mofenson LM. Protecting the next generation – eliminating perinatal HIV-1 infection. *Ibid*: 2316–8 (editorial).

ART to prevent heterosexual transmission of HIV-1

A trial in seven countries of sub-Saharan Africa has provided more evidence about the use of antiretroviral therapy (ART) to prevent transmission of HIV-1 between heterosexual partners.

A post-hoc analysis was performed of data from a trial of aciclovir in people dually infected with herpes simplex virus type 2 and HIV-1. The analysis included 3381 heterosexual couples in Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, and Zambia. During the study 349 subjects with HIV-1 infection began ART at a median CD4 cell count of 198 cells per μ L. There were 103 genetically-linked intra-couple HIV-1 transmissions but only one from an infected partner on ART. The transmission rate was 0.37 per 100 person-years with ART and 2.24 per 100 person-years without ART, a significant 92% reduction in risk. The highest risk was with people not taking ART and with CD4 cell counts <200 cells per μ L. Among couples with an untreated HIV-infected partner with a CD4 cell count >200 cells per μ L 70% of transmissions occurred with plasma HIV-1 concentrations >50 000 copies per ml.

ART reduces the risk of HIV-1 transmission between heterosexual partners. Measurement of CD4 and HIV-1 levels might guide the use of ART.

Donnell D et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010; 375: 2092–8; Dabis F et al. HIV drugs for treatment, and for prevention. *Ibid*: 2056–7 (comment).

Combined antiretroviral treatment and heterosexual transmission of HIV-1

A study in Spain has shown that combined antiretroviral treatment is highly effective in reducing transmission of HIV between heterosexual couples.

The study included 648 stable heterosexual couples in which one partner (the index partner) was known to be infected with HIV. On first testing the prevalence of HIV infection in the other partner was 9.2% when the index partner

was not receiving antiretroviral treatment, 8.7% when the index partner was receiving antiretroviral monotherapy or dual therapy, and zero when the index partner was receiving combined antiretroviral therapy. During follow up of 341 serodiscordant couples in which the infected partner was not on antiretroviral treatment there were 1000 acts of unprotected intercourse (without condom use), 50 pregnancies, and five HIV seroconversions. Condom use reduced the risk of seroconversion by 93%. The index partner was taking combined antiretroviral treatment in 144 couples. In these couples, 7000 unprotected acts of intercourse resulted in 47 pregnancies but no seroconversions.

In this study combined antiretroviral treatment completely prevented HIV transmission.

Del Romero J et al. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. *BMJ* 2010; 340: 1179 (c2205).

Preventing mother-to-child HIV-1 transmission in Botswana

A trial in Botswana included 560 HIV-positive pregnant women with CD4 cell counts of at least 200 cells per cu.mm. Randomisation was to abacavir-zidovudine-lamivudine (AZL) or lopinavir-ritonavir plus zidovudine-lamivudine (LR-ZL) from 26-34 weeks of pregnancy to 6 months after delivery (planned time of weaning). Infants were given single-dose nevirapine and 4 weeks of zidovudine. Virological suppression (<400 copies per ml) at delivery was achieved in 96% (AZL) and 93% (LR-ZL). Suppression throughout breast-feeding was achieved in 92% and 93% of these groups. Among 170 women with cD4 cell counts <200 cells per cu.mm given nevirapine plus zidovudine-lamivudine (observational group) the rate of virological suppression at delivery was 94% and throughout breast feeding 95%. By 6 months of age, 8 of 709 infants (1.1%) were infected with HIV-1 in all three groups. Six of these infants were infected before birth and two during breast-feeding. The rates of treatment-limiting adverse events were 2% (AZL), 2% (LR-ZL), and 11% in an observational group of 170 women on nevirapine plus zidovudine-lamivudine.

These researchers conclude that all HAART regimens from pregnancy to 6 months postpartum were effective.

Shapiro RL et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *NEJM* 2010; 362: 2282-94; Mofenson LM. Protecting the next generation - eliminating perinatal HIV-1 infection. *Ibid*: 2316-8.

Cardiology

High-dose allopurinol for angina

In animal experiments and in patients with cardiomyopathy, allopurinol has been shown to reduce myocardial oxygen demand for a given cardiac output. The mechanism by which it does this is not known. Reduced myocardial oxygen demand might benefit patients with angina. Now a trial in Dundee, Scotland has confirmed this benefit.

The double-blind, placebo-controlled, randomised, crossover trial included 65 patients with stable chronic angina pectoris and angiographically confirmed coronary disease. Randomisation was to allopurinol (increasing gradually from 100 mg once daily to 300 mg twice daily) or placebo for 6 weeks before switching to the other option for a further 6 weeks. The time to ST depression on exercise tolerance testing was 232 seconds at baseline and increased to 298 seconds with allopurinol and 249 seconds with placebo, a significant difference between allopurinol and placebo. Allopurinol also increased total exercise time and time to chest pain significantly compared with placebo. The treatment was well tolerated.

Allopurinol could be a useful, inexpensive, well tolerated and safe anti-ischaemic drug for patients with angina.

Norman A et al. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet* 2010; 375: 2161-7; Antony R, Dargie HJ. Allopurinol for chronic stable angina: old drug, new tricks? *Ibid*: 2126-7 (comment).

Statins not antihypertensive

It has been suggested that as well as lowering cholesterol levels statins might have a blood pressure-lowering effect. Now a study in Italy has shown no such effect. A total of 508 men and postmenopausal women aged 45-70 were randomised at 13 centres to antihypertensive treatment (hydrochlorothiazide 25 mg or fosinopril 20 mg, each daily) with added pravastatin 40 mg, or placebo, daily. None of the patients had a history of cardiovascular events and all had uncontrolled hypertension, hypercholesterolaemia, and asymptomatic carotid artery atherosclerosis. There were significant reductions in clinic, 24 hour, daytime, and night-time systolic and diastolic blood pressures in both groups but less in the pravastatin group. The mean blood pressure never varied by more than 1.9 mmHg between

the two groups.

The addition of a statin had no significant effect on blood pressure.

Mancia G et al. Statins, antihypertensive treatment, and blood pressure control in clinic and over 24 hours: evidence from PHYLLIS randomised double blind trial. *BMJ* 2010; 340: 846 (c1197).

Side-effects of statins: positive and negative

Not enough is known about the positive or negative unintended effects of statin use. Data from a general practice database in England and Wales have been reported. The prospective open cohort study included 225 922 new users of statins and 1 778 770 controls, all aged 30-84 years. Individual statins did not significantly increase the risks of Parkinson's disease, rheumatoid arthritis, venous thromboembolism, dementia, osteoporotic fracture, gastric cancer, colon cancer, lung cancer, melanoma, or cancers of breast or prostate. They did increase the risks of liver dysfunction, acute renal failure, moderate or serious myopathy, and cataract. There was a small protective effect against oesophageal cancer, 8 or 9 cases being prevented for every 10000 patients treated with a statin.

Statins increase the risks of liver dysfunction, renal failure, myopathy, and cataract and reduce the risk of oesophageal cancer.

Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ* 2010; 340: 1232 (c2197); Alsheikh-Ali AA, Karas RH. Balancing the intended and unintended effects of statins. *Ibid*: 1207-8 (editorial).

Oncology

Genetic and environmental factors in breast cancer

Genome analysis has identified several low penetrance breast cancer loci but little is known about interactions between these loci and environmental factors. Researchers in Oxford, England and Paris, France have correlated environmental risk factors and 12 single nucleotide polymorphisms (SNPs) known to be associated with breast cancer.

The study included 7610 women with breast cancer and 10196 controls. The 12 SNPs were correlated with 10 environmental risk factors (age at menarche, parity, age at first birth, breastfeeding, menopausal status, age at menopause, use of hormone replacement therapy

(HRT), BMI, height, and alcohol consumption). None of the 120 comparisons showed evidence of gene-environment interaction. Use of HRT did not affect genotypic relative risks either overall or for oestrogen-receptor-positive breast cancer. Carriers of one high-risk allele were significantly shorter than non-carriers. This study showed no interaction between the 12 SNPs and the 10 environmental risk factors.

Travis RC et al. Gene-environment interactions in 7610 women with breast cancer: prospective evidence from the Million Women Study. *Lancet* 2010; 375: 2143–51; Narod SA. Genes, the environment, and breast cancer. *Ibid*: 2123–4 (comment).

Chemotherapy, amenorrhoea, and survival in early breast cancer

A large multicentre trial in North America has shown that among women with early breast cancer, sequential doxorubicin/cyclophosphamide and docetaxel is better than concurrent treatment with the same drugs, and amenorrhoea during treatment improves survival.

A total of 5351 women with operable, node-positive, early-stage breast cancer were randomised at 185 centres to four cycles of doxorubicin plus cyclophosphamide followed by four cycles of docetaxel (sequential ACT), four cycles of doxorubicin plus docetaxel (DD), or four cycles of doxorubicin, cyclophosphamide, and docetaxel (concurrent ACT). At an average follow-up of 73 months 8-year overall survival was 83% (sequential ACT), 79% (DD), and 79% (concurrent ACT), a significant advantage for sequential ACT over each of the other treatments. The corresponding rates of disease-free survival were 74%, 69%, and 69%. Amenorrhoea for 6 months or longer during treatment was associated with a 24% reduction in overall mortality and a 30% reduction in death or recurrence. This advantage was independent of oestrogen-receptor status or treatment.

Sequential ACT was better than doxorubicin/docetaxel or concurrent ACT and iatrogenic amenorrhoea was associated with improved outcomes.

Swain SM et al. Longer therapy, iatrogenic amenorrhoea, and survival in early breast cancer. *NEJM* 2010; 362: 2053–65; Ellis M. Taxane-based chemotherapy for node-positive breast cancer – take-home lessons. *Ibid*: 2122–4 (editorial).

Diabetes

Screening for type 2 diabetes

The optimum ages for screening for type

2 diabetes and best intervals between screening episodes are not known. The results of mathematical modelling using US data have been reported.

Person-specific data from a representative sample of the US population were used to create a simulated population of 325 000 people aged 30 years without diabetes. Eight screening strategies differing in age at first screening and screening intervals were compared in the mathematical mode. All of these strategies would reduce myocardial infarctions and the microvascular complications of diabetes and increase quality-adjusted life-years (QALYs). Most strategies would reduce mortality but there would be little effect on stroke incidence. The least expensive strategies in terms of cost per QALY were: start at age 30, screen every 3 years (US\$10 512); at 45, every 3 years (\$9731); at 45, every 5 years (\$9786); people with hypertension only, screen every year (\$6287); and people with hypertension, screen every 5 years (\$6490). More expensive strategies would be: at 45, ever year (US\$15 509); at 60, every 3 years (\$25 738); and at 30, ever 6 months to age 75 (\$40 778).

It is concluded that in the USA screening would be cost-effective when including the whole population, started at age 30–45, and repeated every 3–5 years.

Kahn R et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *Lancet* 2010; 375: 1365–74; Rutten G. Screening for type 2 diabetes – where are we now? *Ibid*: 1324–6 (comment).

Blood pressure control in type 2 diabetes

Because of the high associated cardiovascular risk blood pressure control is universally recommended for people with type 2 diabetes but there is little or no evidence about what target blood pressures should be. As part of the ACCORD trial (see above) a target systolic pressure of <140 mmHg has been compared with a target of <120 mmHg. A total of 4733 patients with type 2 diabetes and high cardiovascular risk were randomised to intensive therapy (target systolic blood pressure <120 mmHg) or standard blood pressure control (target <140 mmHg). Mean follow-up was for 4.7 years. At 1 year, the mean systolic blood pressure was 119.3 mmHg (intensive control) vs 133.5 mmHg (standard control). The primary outcome (cardiovascular death or nonfatal myocardial infarction or nonfatal stroke) occurred at

rates of 1.87 and 2.09 per year in the two groups, a nonsignificant 12% reduction in the intensive control group. Annual overall mortality was similar in the two groups (1.28% vs 1.19%). The annual rate of stroke was significantly lower in the intensive control group (0.32% vs 0.53%). Serious adverse events due to antihypertensive treatment occurred in 3.3% vs 1.3%, a highly significant difference.

Intensive blood pressure control did not reduce the rate of the composite outcome significantly.

The ACCORD Study Group. The effects of intensive blood-pressure control in type 2 diabetes mellitus. *NEJM* 2010; 362: 1575–85; Nilsson PM. ACCORD and risk-factor control in type 2 diabetes. *Ibid*: 1628–30 (editorial).

Neurology

Time to treatment for stroke

Two trials have shown early treatment with i.v. recombinant tissue plasminogen activator (rt-PA) after an acute ischaemic stroke to be beneficial but six trials showed no conclusive benefit. Time from stroke onset to treatment is crucial. Now a pooled analysis of eight trials of rt-PA (alteplase) versus placebo (3696 patients) has shown that treatment after more than 4.5 hours may be harmful.

The likelihood of a favourable outcome at 3 months was inversely related to the time from stroke onset to treatment (OTT). No benefit was seen with an OTT of >270 min. The odds of a favourable outcome with alteplase compared with placebo were 2.55 with an OTT of 0–90 min, 1.64 (91–180 min), 1.34 (181–270 min), and 1.22 (271–360 min), all significant in favour of alteplase except at 271–360 min. The occurrence of a large parenchymal haemorrhage was not clearly related to OTT and it occurred in 5.2% in the alteplase group and 1.0% of the controls. The adjusted odds for mortality were 0.78 with an OTT of 0.90 min, 1.13 for 91–180 min, 1.22 (181–270 min) and 1.49 (271–360 min).

After an ischaemic stroke alteplase should be given as soon as possible and is beneficial up to 4.5 hours after stroke onset. After that it could be harmful.

Lees KR et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS and EPITHET trials. *Lancet* 2010; 375: 1695–703; Saver JL, Levine SR. Alteplase for ischaemic stroke – much sooner is much better. *Ibid* 1667–8 (comment).