Oncology

Screening for colorectal cancer

Trials investigating the effectiveness of colorectal cancer (CRC) screening programmes suggest they are effective in reducing CRC mortality. However, more specific questions examining the benefits of sigmoidoscopy and adenoma removal have been examined in two recent trials.

The first trial followed 40 800 patients who had undergone colorectal adenoma removal. The investigators then monitored CRC incidence and mortality. Using CRC rates for the general population, a total of 398 deaths from CRC were expected compared with 383 observed. This yielded a standardised mortality ratio (SMR) of 0.96 among patients who had undergone adenoma removal.

The second trial investigated the effectiveness of flexible sigmoidoscopy on CRC incidence and mortality. Randomised patients received either once-only flexible sigmoidoscopy (n=10 283), or a combination of once-only flexible sigmoidoscopy and faecal occult blood testing (FOBT) (n=10 289). The control group (n=78 220) received no intervention. After a median follow-up of 11 years, 71 participants died of CRC in the screening group versus 330 in the control group (significant hazard ratio (HR), 0.73). No difference in mortality was observed between the sigmoidoscopy and sigmoidoscopy with FOBT. Once-only flexible sigmoidoscopy with or without FOBT reduces both the incidence and mortality of CRC.

Løberg M, Kalager M, Holme Ø, et al. Long-term colorectal-cancer mortality after adenoma removal. *NEJM* 2014; 371: 799–807.
Holme Ø, Løberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: A randomized clinical trial. *JAMA* 2014; 312: 606–15.

Neurology

Nicotinamide for Friedrich's ataxia

Friedrich's ataxia is a genetic, progressive, and degenerative disorder caused by deficiency of the frataxin protein. Currently, no effective disease-modifying treatments exist; however, recent preclinical studies have shown that the histone deacetylase inhibitor nicotinamide (vitamin B3) can induce an increase in frataxin concentrations.

An exploratory, open-label study has investigated the effects of escalating the doses of nicotinamide (from 2 to 8g) in ten patients. The primary outcome measured upregulation of frataxin expression. Results showed that nicotinamide was generally well tolerated; the main adverse event was nausea, which in most cases was mild, and dose-related. Single doses resulted in an increase in the frataxin concentration but after dose escalation a significant and sustained upregulation of frataxin expression was observed. However, clinical measures did not show significant changes.

Nicotinamide increased frataxin concentrations but no changes in clinical measures were observed.

Libri V, Yandim C, Athanasopoulos S. Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study. *Lancet* 2014; 384: 504–13.

Hypothermia for perinatal asphyxia

Perinatal asphyxia encephalopathy is associated with a high risk of death or early neurodevelopmental impairment. Studies have shown that infants treated with moderate hypothermic therapy have improved neurological outcomes at 18 months but crucially, the longer-term neurocognitive benefits remain unknown.

Therefore, the TOBY trial assigned 325 newborns with asphyxial encephalopathy to receive standard care or standard care plus hypothermia to a rectal temperature of 33-34°C for 72 hours. The primary outcome measured survival frequency with an IQ score of 85 or higher in children aged 6-7 years.

Although survival did not differ between the groups, 52% of children receiving hypothermic therapy satisfied the primary outcome compared with 39% in the control group (significant relative risk (RR), 1.31). Further, the intervention group had a reduced risk of cerebral palsy and moderate or severe disability.

Moderate hypothermia after perinatal asphyxia resulted in improved neurocognitive outcomes in middle childhood.

Azzopardi D, Strohm B, Marlow N, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. *NEJM* 2014; 371: 140–9.

Testing for Creutzfeldt-Jakob disease

obtaining a definite diagnosis of the fatal neurodegenerative, Creutzfeldt-Jakob disease is challenging. The commonly used fluorescence assay test, real-time quaking-induced conversion (RT-QuIC), uses cerebrospinal fluid to detect the biomarker, prion protein, and has an estimated 80-90% sensitivity. However, a new study has tested the sensitivity of RT-QuIC analysis of olfactory epithelium from nasal brushings.

The RT-QuIC assays using nasal brushings were positive in 30 of 31 patients with Creutzfeldt-Jakob disease but were negative in 43 of 43 patients without the disease; giving a sensitivity of 97% and a specificity of 100%. By contrast, the RT-QuIC test using cerebrospinal fluid samples from the same patients, had a sensitivity of 77% and a specificity of 100%.

RT-QuIC assays using olfactory epithelium were accurate in diagnosing Creutzfeldt-Jakob disease.

Orrú C, Bongianni M, Tonoli G, et al. A test for Creutzfeldt–Jakob disease using nasal brushings. *NEJM* 2014; 371: 519–29.

Obs & Gyn

Neural tube defect prevention

Research has provided evidence that maternal folic acid supplementation before and during early pregnancy reduces the risk of neural tube defects. However, the optimal population red blood cell (RBC) folate concentration for the prevention of the defects remains unknown.

Two Chinese studies have examined this question by giving 250 000 women of reproductive age folic acid supplementation (400 µg/day) in order to establish the RBC folate concentration at day 28 gestation (time of neural tube closure) and the risk of neural tube defects.

The risk of neural tube defects was high at the lowest estimated RBC folate concentration (25.4 per 10 000 births at 500 nmol/L) but this risk decreased with increasing concentrations and was significantly attenuated at concentrations above 1000 nmol/L (6 per 10 000).

Higher RBC folate concentrations reduced the risk of neural tube defects. Therefore, these concentrations could be used as a risk biomarker.

Crider K, Devine O, Hao L, et al. Population red blood cell folate concentrations for prevention of neural tube defects: Bayesian model. *BMJ* 2014; 349: 4554.

Antiepileptic drugs, spontaneous abortion, and stillbirth

Anti-epileptic drug use during pregnancy

has been associated with pre-eclampsia, and foetal malformations. However, little is known about the association between antiepileptics in pregnancy and spontaneous abortion or stillbirth. Therefore a population study aimed to establish the risks of spontaneous abortion and stillbirth after use of antiepileptic drugs during pregnancy.

The study results indicated that pregnant women using anti-epileptics had a 13% higher risk of spontaneous abortions than women not using antiepileptics. However, the risk of spontaneous abortion was not increased in women taking antiepileptics with an epilepsy diagnosis, only in women taking antiepileptics without a diagnosis of epilepsy. In women who had multiple pregnancies with discordant antiepileptic drug use, no increased risk of abortion for exposed pregnancies was observed. Antiepileptics were not associated with an increased risk of stillbirths.

No association between the use of antiepileptic drugs and spontaneous abortion or stillbirth was found.

Bech B, Kjaersgaard M, Pedersen H, et al. Use of anti-epileptic drugs during pregnancy and risk of spontaneous abortion and stillbirth: population based cohort study. *BMJ* 2014; 349: 5159.

Diagnostic accuracy of foetal *RHD* status

Postnatal prophylaxis with anti-RhD immunoglobulin reduces the prevalence of foetus and newborn haemolytic disease. Foetal *RHD* genotyping can be done during the pregnancy but techniques are labour-intensive so genotyping is only performed in high-risk mothers. Recently, new developments in *RHD* genotyping has reduced labour requirements and mass testing of foetal DNA may be possible.

A recent study analysed the accuracy of mass *RHD* genotyping by performing it on 2288 *RHD*-negative women up to four times during pregnancy (from 11 weeks) and comparing its accuracy with *RHD* status determined by cord blood serology results.

The sensitivity for the detection of *RHD* positivity was 96.9% at <11 weeks gestation, and over 99.7% between 11 and 23 weeks, whereafter it was 100%. Before 11 weeks gestation, 1.9% of babies tested were falsely predicted as *RHD* negative.

After 11 weeks, mass foetal *RHD* genotyping is accurate for the prediction of *RHD* type.

Chitty L, Finning K, Wade A, et al. Diagnostic accuracy of routine antenatal determination of fetal RHD status across gestation: population based cohort study. *BMJ* 2014; 349: 5243.

Cardiovascular

Sodium consumption and cardiovascular death

High sodium intake increases blood pressure, a risk factor for cardiovascular disease. Yet the effects of sodium intake on global cardiovascular mortality are uncertain.

A recent study compiled data from research conducted worldwide examining sodium intake and its effect on blood pressure and cardiovascular mortality.

Guidelines recommend sodium intake should not exceed 2 g per day. However, in 2010, 88% of the global adult population exceeded this with calculations estimating a mean daily intake of 3.95 g (with regions ranging from 2.18 to 5.51 g). Annually, 1.65 million deaths from cardiovascular causes were attributed to excessive sodium intake (10% of all cardiovascular causes of death). A total of 84% of these deaths occurred in low- to middle-income countries.

A significant proportion of cardiovascular deaths are caused by excessive sodium intake.

Mozaffarian D, Fahimi S, Singh G, et al. Global sodium consumption and death from cardiovascular causes. *NEJM* 2014; 371: 624–34.

Angiotensin-neprilysin inhibition for heart failure

The drug, LCZ696, is comprised of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker (ARB) valsartan. It was recently found to be successful in treating hypertension, or heart failure with a preserved ejection fraction than an ARB alone. A recent trial compared the efficacy of LCZ696 at reducing death from cardiac causes or hospitalisation among patients with heart failure and a reduced ejection fraction (≤40%).

A total of 8442 patients were randomly assigned to receive either LCZ696 (200 mg twice daily) or enalapril (10 mg twice daily). Importantly, the trial was stopped early due to an overwhelming benefit of LCZ696. After a median follow-up of 27 months, 17% of patients receiving LCZ696 had died compared with 20% in the enalapril group (significant HR for LCZ696 group, 0.84). LCZ696 also reduced the risk of hospitalization for heart failure by 21% in addition to decreasing symptoms.

LCZ696 was superior to enalapril in reducing the risks of death and hospitalisation for heart failure.

McMurray J, Packer M, Desai A, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *NEJM* 2014; 371: 993–1004.

Clarithromycin and risk of cardiac death

Acute cardiac toxicity is an increasingly recognised potential adverse effect of antimicrobial treatment, particularly macrolides such as erythromycin and azithromycin. However, relatively little is known about the cardiovascular risks associated with other macrolides.

A Danish study assessed the risk of cardiac death among patients prescribed clarithromycin and roxithromycin and compared the risk in those receiving penicillin V.

The incidence of cardiac death for those patients receiving clarithromycin was 5.3 per 100 person years compared with 2.5 per 100 person years for penicillin V – a significantly increased risk. However, no increased risk of cardiac death was observed for roxithromycin. Despite this, the absolute risk remains small and therefore should have limited, if any, effect on prescribing practice.

Clarithromycin is associated with a minor increased risk of cardiac death.

Svanstrom H, Pasternak B, Hviid A. Use of clarithromycin and roxithromycin and risk of cardiac death: cohort study. *BMJ* 2014; 349: 4930.

Paediatrics

Erythropoietin for preterm infants

Premature infants are at risk of developing encephalopathy of prematurity which is associated with long-term neurodevelopmental delay. Imaging show characteristic brain changes such as white matter loss, lesions, and abnormal cortical development. Studies have shown erythropoietin to be neuroprotective and to have beneficial effects on neurodevelopment.

A recent trial randomised preterm infants to receive either three intravenous infusions of high-dose recombinant human erythropoietin (n=77) or placebo (n=88) before 42 hours after birth. Although neurodevelopment was not assessed, the authors compared MRI brain images of subjects in the intervention and placebo groups. Results showed that significantly fewer infants treated with erythropoietin had abnormal scores for white matter injury (risk ratio, 0.58), white matter signal intensity (risk ratio, 0.20), periventricular white matter loss (risk ratio, 0.53), and grey matter injury (risk ratio, 0.34).

High-dose erythropoietin within 42 hours after birth reduced the risk of

brain abnormality on MRI.
Leuchter R, Gui L, Poncet A, et al. Association between early administration of high-dose erythropoietin in preterm infants and brain MRI abnormality at term-equivalent age. *JAMA* 2014; 312: 817–24.

Validation of Apgar scoring

The Apgar score has been used as an index of early neonatal condition for over 50 years, but with advances in healthcare, some have questioned its relevance. Therefore, a recent study has assessed the strength of the relation between Apgar score at 5 min and the risk of neonatal and infant mortality.

Data for 1 029 207 births with a gestational age of 22-44 weeks were retrospectively assessed to calculate the relative risks of neonatal and infant death in neonates and infants with low (0-3) and intermediate (4-6) Apgar scores.

Compared with normal Apgar scores (7-10), low Apgar scores at 5 min were associated with an increased risk of neonatal and infant death across all gestational ages. The relative risk for early neonatal death was 359; 31 for late neonatal death; and 50 for infant death.

Low Apgar score was strongly associated with the measured risk of neonatal or infant death.
Iliodromiti S, Mackay D, Smith G, Pell J, and Nelson S. Apgar score and the risk of cause-specific infant mortality: a population-based cohort study. *Lancet* 2014; doi:10.1016/50140-6736 (14) 61135-1.

Pulse oximetry for congenital heart disease screening

Pulse oximetry screening for the detection of congenital heart disease (CHD) in high-income countries has proven beneficial. However, whether the benefits of this can be translated to low-income countries is unknown.

A Chinese study assessed whether the accuracy of pulse oximetry plus clinical assessment in newborns was effective in the detection of CHD. Babies with an abnormal result from either assessment were then referred for echocardiography. False-negative results were identified by clinical follow-up and parent feedback.

During the prospective phase, 122 738 consecutive newborns were screened (2031 were symptomatic), of which 1071 babies were identified to have CHD. In asymptomatic newborns, the sensitivity of pulse oximetry was 93.2% for critical CHD. The addition of pulse oximetry to clinical assessment improved sensitivity for detection of critical CHD from 77·4% to 93·2%.

Pulse oximetry plus clinical assessment is feasible and reliable for the detection of major CHD in newborns.
Zhao Q, Ma X, Ge X, et al. Pulse oximetry with clinical assessment to screen for congenital heart disease in neonates in China: a prospective study. *Lancet* 2014; 384: 747–54.

A strategy to reduce neonatal and infant morbidity

The Integrated Management of Neonatal and Childhood Illness (IMNCI) strategy incorporates health worker home visits, whilst improving management of the sick child and strengthening health systems. The aim is to reduce neonatal and infant morbidity by changing treatment-seeking practices.

A recent study included over 60 000 births from 18 population clusters in India. Each was randomised to receive either IMNCI or no intervention. The primary outcome measured the effect of IMNCI on treatment-seeking practices.

Subjects in the intervention clusters reported fewer episodes and sought treatment more often for severe neonatal illness, but also for local neonatal infection, diarrhoea, and pneumonia. Infants in the intervention clusters were more likely to be exclusively breast fed in the sixth month of life.

The implementation of IMNCI was associated with timely treatment seeking and reduced morbidity. This is likely to explain the observed reduction in mortality.
Mazumder S, Taneja S, Bahl R, et al. Effect of implementation of Integrated Management of Neonatal and Childhood Illness programme on treatment seeking practices for morbidities in infants: cluster randomised trial. *BMJ*. 2014; 349:4988.

Tuberculosis

Moxifloxacin-based regimens for tuberculosis

Short-term tuberculosis treatment regimens could improve rates of adherence and adverse effects. Moxifloxacin, a fluroquinolone, may facilitate this as it induces a rapid decline in bacterial load. Consequently, a non-inferiority study aimed to determine if replacement of isoniazid or ethambutol with moxifloxacin would be effective over 4 months rather than the standard 6 month regimen.

The control group (n=510) received isoniazid, rifampin, pyrazinamide, and ethambutol for 8 weeks, followed by 18 weeks of isoniazid and rifampin. In the isoniazid group (n=514), ethambutol was replaced with moxifloxacin for 17 weeks. In the ethambutol group (n=524), isoniazid was replaced with moxifloxacin for 17 weeks (ethambutol group). The primary outcome measured treatment failure or relapse within 18 months.

Fewer patients in the isoniazid and the ethambutol groups had a favourable outcome (85% and 80%, respectively) compared with 92% in the control group. Therefore shortening treatment to 4 months was not effective.
Gillespie S, Crook A, McHugh T, et al. Four-month moxifloxacin-based fegimens for drug-sensitive tuberculosis. *NEJM* 2014.

Tuberculous pericarditis therapy

Tuberculous pericarditis is associated with a high morbidity and mortality even after antituberculosis therapy. A recent randomised trial evaluated the efficacy of adjunctive glucocorticoid therapy and *Mycobacterium indicus pranii* immunotherapy (which is thought to reduce tuberculosis inflammation and increase CD4+ count in HIV patients).

A total of 1400 patients with definite or probable tuberculous pericarditis were randomised to receive either prednisolone or placebo for 6 weeks and to either *M. indicus pranii* or placebo injections for 3 months. The primary outcome was a composite of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis.

By the study endpoint, there was no significant difference in the primary outcome between patients who received prednisolone and those who received placebo (23.8% and 24.5, respectively) or between those who received *M. indicus pranii* immunotherapy or placebo (25.0% and 24.3% respectively).

Neither prednisolone nor *M. indicus pranii* immunotherapy had a significant beneficial effect on tuberculous pericarditis.
Mayosi M, Ntsekhe M, Bosch J, et al. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. *NEJM* 2014; 371: 1121–30.

Izoniazid plus antiretroviral therapy for tuberculosis prevention

Antiretroviral therapy (ART) reduces the risk of developing tuberculosis, but new evidence has indicated that dual ART and isoniazid treatment may further reduce this risk. Therefore a recent South African trial assessed the efficacy and safety of this dual therapy at reducing the risk of developing tuberculosis in subjects infected with HIV-1.

CPD Challenge

See page 54 to test yourself on this article

A total of 1329 patients were randomised to receive either isoniazid or placebo for 12 months alongside concurrent ART.

After 3227 person-years of follow-up, 95 incident cases of tuberculosis were recorded, of which 37 occurred in the isoniazid group compared with 58 in the placebo group – yielding a significant hazard ratio of 0.63. Of note, raised alanine transaminase concentrations caused drug discontinuation in 19 of the isoniazid group versus 10 in the placebo group.

Isoniazid preventative therapy should be recommended to all patients receiving ART in moderate or high incidence tuberculosis areas.

Rangaka M, Wilkinson R, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet* 2014; 384: 682–90.

Effect of BCG vaccination against *Mycobacterium tuberculosis*

The BCG vaccine has been the subject of numerous efficacy trials over the decades. A recent systematic review and meta-analysis aimed to determine whether the BCG vaccination protects against *Mycobacterium tuberculosis* when assessed by interferon γ release assays in children.

A total of 14 studies incorporating 3855 participants were included in the primary analysis. The estimated overall risk ratio was 0.81, indicating a protective efficacy of 19% against infection among vaccinated children after exposure compared with unvaccinated children. Further analysis, that included information on progression to active tuberculosis at the time of screening, showed protection against infection was 27% (RR, 0.73) compared with 71% (RR, 0.29) against active tuberculosis. Among those infected, protection against progression to disease was 58% (RR, 0.42).

BCG protects against *M tuberculosis* as well as progression from infection to disease.

Roy A, Eisenhut M, Harris RJ, et al. Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in children: systematic review and meta-analysis. *BMJ* 2014; 349: 4643.

Infection

Male circumcision for HIV prevention

Evidence suggests that male circumcision reduces men's risk of HIV acquisition by 50-60%. Despite rates of voluntary medical male circumcision (VMMC) rising in Kenya, they remain considerably short of targets. A recent Kenyan trial assessed whether giving economic incentives to volunteers would increase the VMMC prevalence.

A total of 1504 volunteer men were randomised to one of three groups before undergoing circumcision. Three groups received compensation in the form of food vouchers. The first group received 200 Kenya shillings (≈US $2.50); the second, 700 Kenya shillings; and the third group received 1200 Kenya shillings. The control group received no compensation.

At 2 months, analysis showed VMMC uptake was highest in the third group (9%) compared with 6.6% in the second and 1.9% among those in the first group. The control group uptake was 1.6%.

Economic incentives resulted in a modest increase in the prevalence of circumcision.

Thirumurthy H, Masters SH, Rao S, et al. Effect of providing conditional economic compensation on uptake of voluntary medical male circumcision in Kenya: A randomized clinical trial. *JAMA* 2014; 312(7): 703–11.

Combined treatment for neurocysticerosis

Neurocysticerosis caused by *Taenia solium* is regarded as the most frequent cause of acquired epilepsy worldwide. Current treatment utilises praziquantel or albendozole but this has suboptimum efficacy. However, recently a trial assessed the effectiveness of these drugs in combination.

A total of 124 patients were randomly assigned to receive either albendazole (15 mg/kg per day) plus praziquantel (50 mg/kg per day), increased dose albendazole (22 mg/kg/day), or standard dose albendazole (15 mg/kg per day). The primary outcome assessed complete cyst resolution on 6-month MRI.

Enrolment was stopped after interim analysis showed superiority of the combined therapy. At 6 months, 64% of patients in the combined group had complete cyst resolution compared with 37% in the standard albendazole and 53% in the increased albendazole groups. No significant difference in the reported adverse effect rates was observed.

Albendazole plus praziquantel increases the parasiticidal effect in patients with brain cysticerosis cysts.

Garcia H, Gonzales I, Lescano A, et al. Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomised controlled trial. *Lancet Infectious Diseases* 2014; 14: 687–95.

See page 54 for questions about this article