Paediatrics

Social communication therapy in autism

Autism is an enduring disorder with great emotional and lifetime costs that comes with a prevalence of 1% in children. Currently, there is limited literature on the impact of early intervention on long-term outcomes in autism symptoms.

PACT was the largest trial to investigate the effect of intervention on autistic children. It used parent-mediated social communication intervention with children who had core autism aged 2 to 4 years. A follow-up of the UK-based study has been done to determine long-term outcomes of the PACT trial. At an average of five years from the PACT trial endpoint, 80% of the original 152 participants were traced and assessed. Over the five-year period up to the point of re-contact there was an overall significant reduction in symptom severity.

These findings are the first to show the efficacy of early intervention in children with autism, supporting the clinical value of the PACT trial.

Pickles A, Le Couteur A, Leadbitter K, et al. Parent-mediated social communication therapy for young children with autism (PACT): long-term follow-up of a randomised controlled trial. *The Lancet* 2016; 388: 2501–2509.

Oral dextrose gel for neonatal hypoglycaemia

The long-term effects of neonatal hypoglycaemia can be severe. Approximately 15% of newborns will be affected and currently the only recommended prophylaxis is early feeding.

A double-blind, randomised study was set out to determine what dose of 40% oral dextrose could best prevent neonatal hypoglycaemia. Newborns at risk of hypoglycaemia (n=416) were randomised within four groups plus corresponding placebo, receiving 40% dextrose at either 200mg/kg or 400mg/kg either at one dose at one hour or followed with three doses of 200mg/kg. Risk criteria for hypoglycaemia included diabetic mothers, late-preterm delivery and small or large birthweight.

Single dose at 200mg/kg provided the lowest risk of hypoglycaemia (p=0.04) compared to placebo. Any dose of dextrose decreased risk of hypoglycaemia and there were no significant differences in risk reduction between dose groups. Single doses accounted for better tolerance in infants than multiple doses and were easier to manage.

Oral dextrose gel is effective in decreasing risk of neonatal hypoglycaemia when given at a single dose of 200mg/kg.

Hegarty JE, Harding JE, Gamble GD, et al. Prophylactic oral dextrose gel for newborn babies at risk of neonatal hypoglycaemia: A randomised controlled dose-finding trial (the Pre-hPOD Study). *PLoS Med* 2016; 13(10): e1002155. DOI:10.1371/journal.pmed.1002155

Risk factors for childhood stunting

In the developing world, an estimated 30% of children suffer with stunted growth, a disorder with poor health and developmental outcomes that is associated with 14% of childhood deaths. In order to better understand growth stunting, a group of researchers have carried out a comparative risk assessment analysis on risk factors.

Risk factors were categorised into five main groups: maternal nutrition and infection; teenage motherhood and short birth intervals; foetal growth restriction and preterm birth; child nutrition and infection; and environmental factors.

Worldwide, the leading risk factor for stunted growth was being born at term but at a small weight, accounting for over 10 million cases of the 44 million total. Poor sanitation followed, responsible for seven million of the cases, and diarrhoea came third.

This study suggests efforts to combat stunting should focus on ways to prevent foetal growth restriction — one of the leading causes of childhood stunting in developing countries.

Danaei G, Andrews KG, Sudfeld CR, et al. Risk Factors for childhood stunting in 137 developing countries: A comparative risk assessment analysis at global, regional, and country levels. *PLoS Med* 2016; 13(11): e1002164. doi:10.1371/journal.pmed.1002164

Timing of allergenic food introduction

Introduction of allergenic foods is one method for decreasing the risk of developing food allergies.

However, optimum timings of allergen introduction to an infant's diet are not yet clear and indeed there have been confounding studies adding to the uncertainty. To help provide guidance on this for the UK Food Standards Agency, a systematic review and meta-analysis has been conducted. Data were extracted from 146 studies and evidence of allergic or autoimmune diseases were used as a primary endpoint.

Moderate-certainty evidence from five trials and over 1900 patients demonstrated that egg introduction for infants aged 4 to 6 months was successful in reducing egg allergy (p=0.009). Two trials involving over 1500 participants demonstrated a significantly reduced peanut allergy risk (p=0.009) when introduced at 4 to 11 months. The timing of introduction of these allergens had no association with risk of allergy to other foods.

Early dietary introduction of eggs and peanuts is associated with a significantly reduced risk of developing an allergy to these foods.

Ierodiakonou D, Garcia-Larsen V, Logan A, et al. Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: A systematic review and meta-analysis. *JAMA* 2016; 316: 1181–1192.

Infection

Impact of meningitis B vaccine schedule

In September 2015 the UK became the first country to introduce the 4CMenB vaccine into the publicly funded two-dose infant vaccination scheme against meningitis B (MenB). This is a move that has faced some reluctance from other countries for reasons including high cost of drug and safety, and efficacy uncertainties. A study has been funded by Public Health England to assess the effectiveness of the vaccine schedule since it was introduced. Impact of the vaccine was assessed by comparing MenB cases in vaccinated children with cases in equivalent cohorts four years before vaccine introduction, and in children ineligible for the vaccine. Vaccine efficacy in children who had received both doses was over 82% against all MenB cases. There was a 50% incidence rate ratio reduction in MenB cases compared to pre-vaccination periods for those children eligible for vaccine.

In the first 10 months of the 4CMenB vaccination programme MenB cases halved for vaccinated children, demonstrating a promising step in the fight against meningitis B.

Parikh SR, Andrews NJ, Beebeejaun K, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. *The Lancet* 2016; 388: 2775–2782.

Candidate for Ebola infection

Within the high-pressure environment of finding a suitable treatment for Ebola, primate studies have identified a promising candidate. A randomised control trial has been conducted to assess the potential for ZMapp, a triple monoclonal antibody therapy. Patients

with PCR-confirmed Ebola virus disease (EVD) were randomly assigned 1:1 to either receive standard of care alone or standard of care plus three infusions of ZMapp. The primary endpoint of death by 28 days was 30% over the whole study. In the standard of care alone setting (n=35) 13 patients died (37%) and eight out of 36 patients (22%) in the standard of care plus ZMapp setting had died at 28 days. These results fell short of a pre-determined statistical threshold for efficacy within the study.

Despite the observed benefit of ZMapp, combined therapy of this drug with standard of care did not meet the trials requirement for superiority in the treatment of Ebola.

The PREVAIL II Writing Group, for the Multi-National PREVAIL II Study Team. A randomized, controlled trial of ZMapp for Ebola virus infection. *NEJM* 2016; 375: 1448–1456.

Seasonal malaria chemoprevention for children

The seasonal malaria chemoprevention (SMC) programme gives children under five living in areas of highly seasonal malarial transmission a schedule of sulfadoxine-pyrimethamine with amodiaquine each month during the high season. With consideration for the high burden found in older children who do not meet the SMC criteria, a study has been done to determine the efficacy of SMC for children up to 10 years of age to assess the benefits of expanding the SMC. For this study, SMC was introduced to children 10 years and younger in three districts within central Senegal over a three-year period. Malaria case notice and death information were provided from outpatient clinics and a surveillance system, respectively.

For children aged 10 years and below the introduction of SMC significantly reduced malaria incidence by 60% and cases of severe malaria by 45%. No difference in all-cause mortality was observed with the introduction of SMC.

SMC provides means for a tolerable and effective seasonal anti-malarial programme for children aged up to 10-years-old.

Cissé B, Ba EH, Sokhna C, et al. Effectiveness of seasonal malaria chemoprevention in children under ten years of age in Senegal: A stepped-wedge cluster-randomised trial. *PLoS Med* 2016; 13(11): e1002175. DOI: 10.1371/journal.pmed.1002175.

S.mansoni infection and immunisation efficacy

The presence of a schistosomiasis infection can create an immune environment that can compromise response to vaccination. One team wanted to know if existing infection with *Schistosomiasis mansoni* at the time of vaccination against hepatitis B and tetanus toxoid would affect efficacy of the vaccine.

A total of 146 individuals were included in the analysis, 26% of which were found to be positive for *S. mansoni*. Over an eight-month period blood samples were taken and immune status was analysed. The study found that schistosomiasis infection alone did not significantly alter either vaccine's efficacy in the period soon after immunisation. however, over time *S. mansoni*-positive individuals demonstrated a rapid decrease in antibodies against the tetanus toxoid compared to non-schistosomiasis infected individuals, suggesting a declining effect of protective antibodies against tetanus and waning effect of vaccine.

There may be some increased risk of compromising vaccine-derived immune status in individuals with schistosomiasis.

Riner DK, Ndombi EM, Carter JM, et al. Schistosoma mansoni infection can jeopardize the duration of protective levels of antibody responses to immunizations against hepatitis B and tetanus toxoid. *PLoS Negl Trop Dis* 2016; 10(12): e0005180. DOI: 10.1371/journal.pntd.0005180

Gastroenterology

Ustekinumab for Crohn's Disease

Ustekinumab, a monoclonal antibody, has been put into a phase 3 study to test its efficacy in the treatment of Crohn's disease.

Participants were moderate to severe Crohn's sufferers with a history of poor response or tolerance to the usual therapies. The trial began as two eight-week induction studies with over 1300 participants randomly assigned to receive intravenous ustekinumab at either 130mg or 6mg/kg, or placebo.

Participants who responded (n=397) entered a 44-week maintenance trial and were randomised to receive either subcutaneous injections of 90mg ustekinumab every eight or 12 weeks or placebo.

Primary endpoints for the induction and maintenance trials were clinical response at week six and remission at week 44, respectively. Both induction studies found a significantly higher response rate for those on both drug doses compared with placebo. The maintenance study demonstrated a significantly higher remission rate at 44 weeks for both treatment intervals compared to placebo.

Among Crohn's sufferers ustekinumab was effective at maintaining remission in patients who responded well to induction therapy.

Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for crohn's disease. *NEJM* 2016; 375: 1946–1960.

First-line treatment for *H. pylori*

Infection with *Helicobacter pylori* is linked to an increased risk of gastric cancers. However, its standard triple therapy has experienced a decreasing efficacy with the emergence of antibiotic resistance. This has urged research into alternative strategies, including use of a second-line therapy, bismuth, as a first-line treatment. A superiority trial has compared three first-line options for the treatment of *H. pylori*. Efficacy and safety comparisons were conducted on 10-day concomitant therapy, 10-day bismuth quadruple therapy, and 14-day triple therapy. Over 1600 *H. pylori*-positive patients from nine medical centres in Taiwan were randomly assigned either of the three treatments in a 1:1:1 ratio. Eradication rates for concomitant, bismuth and triple therapies were 86%, 90% and 84%, respectively. The 10-day bismuth quadruple therapy was found to be significantly superior (p=0.001) to the 14-day triple therapy, but not to the 10-day concomitant therapy setting. Frequency of adverse events was lowest in the 14-day triple therapy setting.

Bismuth quadruple therapy given for 10 days appears preferable as a first-line treatment for *H. pylori*.

Liou J, Fang Y, Chen C, et al. Concomitant, bismuth quadruple, and 14-day triple therapy in the first-line treatment of Helicobacter pylori: a multicentre, open-label, randomised trial. *The Lancet* 2016; 388: 2355–2365.

Sanitation facility access and diarrhoeal disease

In developing countries, diarrhoeal disease is one of the leading causes of death in children for which sanitation and access to clean water are major risk factors. Unshared household access to sanitation facilities has been included in the Millennium Development Goal (MDG) criteria. However, there has been talk of adjusting these criteria to include access to facilities shared by five or fewer households. To assess if sharing facilities contributes to childhood moderate-to-severe diarrhoea (MSD), a matched case-control study has analysed data from the Global Enteric Multicentre Study. Data from seven sites including over 8500 case children were matched to 12 300 control children. Children

sharing facilities with two or more households experienced a significantly increased risk of MSD compared to children with access to an unshared sanitation facility. This difference was found in Kenya, Mali, Mozambique, and Pakistan, but not in The Gambia, Bangladesh or India.

There is an increased risk of MSD in children sharing sanitation facilities and this should be considered in the MDG criteria.

Baker KK, O'Reilly CE, Levine MM, et al. Sanitation and hygiene-specific risk factors for moderate-to-severe diarrhoea in young children in the Global Enteric Multicenter Study, 2007–2011: Case-control study. *PLoS Med* 2016; 13(5): e1002010. DOI:10.1371/journal.pmed.1002010

Prevention of colorectal cancer following neoplasia

The current method for monitoring the high-risk of developing sporadic colorectal cancer following colorectal neoplasia is through screening colonoscopy. However, this is a poorly adhered-to approach. Subsequently, researchers have investigated the potential of pharmaceutical intervention as a means of advanced neoplasia prevention in a systematic review and meta-analysis looking at efficacy and safety of several candidate drugs. Studies included in the analysis were randomised controlled trials involving participants with previous neoplasia, followed up with candidate drugs. The study included 15 trials and over 12 200 patients looking at 10 alternative preventative candidates. The analysis revealed non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDS) were the best at prevention. This was followed by aspirin (low-dose) which was also found to be the safest option. High-dose aspirin had a reduced safety profile but similar efficacy to low-dose aspirin.

In the prevention of advanced neoplasia following benign colorectal neoplasia non-aspirin NSAIDs may be the most effective option, followed closely by the comparatively safer low-dose aspirin.

Dulai PS, Singh S, Marquez E, et al. Chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia: systematic review and network meta-analysis. *BMJ* 2016; 355 :i6188.

HIV

Worm burden and HIV risk

There is some suggestion that helminth infection may increase HIV susceptibility by creating a host immune environment that facilitates HIV acquisition. To assess this relationship a study has looked at the effect of lymphatic filariasis, a disease caused by the helminth *Wuchereria bancrofti*, on HIV incidence in Southwest Tanzania. The EMINI study was a population-based cohort study that enrolled around 18 000 participants. Individuals were tested for HIV and filarial antigen, an indicator of worm infection, and followed up to assess HIV infection rates in those positive or negative for lymphatic filariasis. Incidence of newly acquired HIV infection was found to be significantly higher in individuals already positive for lymphatic filariasis compared to those without helminth infection. When controlled for other known HIV risk factors, including sexual behaviour, filariasis infection persisted as an independent and significant risk factor for HIV acquisition.

There is an observed increased risk of HIV associated with helminth burden that may be due to host immune response.

Kroidl I, Saathoff E, Maganga L, et al. Effect of Wuchereria bancrofti infection on HIV incidence in southwest Tanzania: a prospective cohort study. *The Lancet* 2016; 388: 1912–1920.

Antiretroviral therapy in perinatal HIV prevention

The most safe and efficacious treatment regimens in the prevention of mother-to-child transmission of HIV are not well defined.

The PROMISE randomised trial aimed to build-up information in this area by comparing transmission rates and safety in participants over three treatment settings. Participants included over 3000 HIV-infected women at 14 plus weeks' gestation. Enrolled women were given zidovudine and single-dose nevirapine, followed by a post-partum regimen of zidovudine alone; zidovudine-based antiretroviral therapy (ART); or tenofovir-based ART.

A significantly lower rate of HIV transmission to infants was found in both ART-based groups compared to the zidovudine-alone setting. HIV-free survival was found highest in infants from the zidovudine-based ART setting. However, adverse maternal and infant effects were observed at higher rates for both ART-based groups compared to zidovudine alone. These included higher rates of preterm delivery and low birthweight.

Antenatal ART was responsible for lower HIV transmission to infants compared to zidovudine, but higher adverse maternal and neonatal outcomes should be important considerations in the management of HIV-compromised pregnancies.

Fowler MG, Qin M, Fiscus SA, et al. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. *NEJM* 2016; 375: 1726–1737.

Barriers for adherence to antiretrovirals

One of the major challenges facing HIV treatment comes from poor adherence with antiretroviral therapies (ART). One group has set up a review to identify the key barriers that prevent adherence with hope of targeting interventions to improve future adherence. Data was extracted from 125 studies that provided adherence-barrier information. Populations investigated included over 1700 adults, 1000 children and 800 adolescents. Analysis revealed that the most frequent barriers to adherence across all age groups included forgetting, being away from home and changes to daily routine. Feeling sick appeared to be a more common barrier to adherence than feeling well. Depression appeared as a reason for poor adherence in over 15% of all cases. Substance and alcohol abuse was a common barrier among adults. And secrecy was found to be reported by more than 10% of adults and children.

Identification of these common barriers to adherence of ART may help develop better targeted strategies for at-risk individuals to improve ART adherence.

Shubber Z, Mills EJ, Nachega JB, et al. Patient-reported barriers to adherence to antiretroviral therapy: A systematic review and meta-analysis. *PLoS Med* 2016; 13(11): e1002183. DOI: 10.1371/journal.pmed.1002183

Vaginal ring containing antiretroviral

There is strong evidence for the use of prophylactic antiretrovirals for HIV prevention. These results, however, have not been replicated in trials with African women. The likelihood is that this is due to poor adherence. To combat this, simpler methods of prophylaxis may be better adhered to and therefore provide more protection. A phase 3, double-blind study investigated the use of vaginal rings containing the antiretroviral dapivirine in preventing HIV in women aged 18 to 45.

Over 2600 women were enrolled across Malawi, South Africa, Uganda, and Zimbabwe, and were randomised to a monthly vaginal ring containing dapivirine or placebo. Of these a total of 168 HIV infections occurred during follow-up. A 27% lower incidence of HIV was observed in the dapivirine group (p=0.046). The result was shown to be even more significant when

analysis excluded two groups with evidence of poor adherence and the incidence decreased by 37% compared to placebo (p=0.007).

Antiretroviral containing monthly vaginal rings may provide increased protection against HIV due to increased adherence.

Baeten, JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *NEJM* 2016; 375: 2121–2132.

Misc

Neurologic disorder from potential analgesic

Fatty acid amide hydrolase (FAAH) inhibitors are being investigated for their use as potential analgesics. These properties have so far been demonstrated in animal models with FAAH inhibition shown to enhance natural analgesic cannabinoid-like substances.

A phase 1 study has investigated the safety of a reversible FAAH inhibitor in healthy volunteers.

Dose safety was assessed giving single doses and repeated oral doses for 10 days in 84 volunteers with no reported adverse events. A further cohort of six participants (with four consented to data use) were assigned to the highest trialled dose of 50mg/day. After a period of five days a rapid and unanticipated set of severe neurological impairments occurred in three of four volunteers. Features included headache, memory deficit and altered consciousness.

One volunteer remained asymptomatic, two patients recovered, albeit with residual memory impairment in one and residual cerebellar syndrome in the other, and the fourth patient subsequently became brain dead.

So far the mechanisms underlying these neurological symptoms is unknown.

Kerbrat A, Ferré J, Fillatre P, et al. Acute neurologic disorder from an inhibitor of fatty acid amide hydrolase. *NEJM* 2016; 375: 1717–1725.

Psychotropic medications for violent crimes

Violent reoffending crimes are common among released prisoners and existing interventions are poor. Psychiatric and substance abuse disorders are overrepresented among the prison population and subsequently the potential for using psychotropic drugs as an intervention is being explored as a method of reducing violent reoffending.

A cohort study has been conducted to investigate if psychotropic medications decrease the risk of violent reoffending among released prisoners. This study focused on the main psychotropic drugs prescribed to prisoners and analysis was performed on rates of violent reoffending in released prisoners when medicated, compared to rates of violence in non-medicated periods within-individual analyses. All prisoners released in Sweden between 2005 and 2010 were followed up for an average of four years.

Released prisoners experienced lower rates of violent reoffending during periods on psychotropic medications compared to periods off treatment. When appropriate, antipsychotics, psychostimulants, and drugs used in addictive disorders have potential for reducing the risk of violent reoffending among released prisoners.

Chang Z, Lichtenstein P, Långström N, et al. Association between prescription of major psychotropic medications and violent reoffending after prison release. *JAMA* 2016; 316(17): 1798–1807.

Economic burden of physical inactivity

Physical inactivity is regarded as one of the major worldwide drivers of both morbidity and mortality. The economic value of which remains to be worked out. One study has attempted to quantify a global representative of the economic burden of physical inactivity. Compiling data available from over 140 countries and 93% of the world's population, healthcare costs and disability-adjusted life years (DALYs) were estimated along with productivity losses. Non-communicable diseases (NCDs) attributable to lack of physical activity were assessed.

For 2013, an estimated worldwide cost of over US$58 billion was used to cater for the burden of physical inactivity, over half of which was paid for by the public. Inactivity-related deaths contributed to over $13 billion in productivity losses, as well as a total of 13 million DALYs.

The figure that this study provides for the economic burden of physical inactivity should help justify prioritisation for promotion of physically active lifestyles worldwide, with hope of reducing the burden of NCDs.

Ding D, Lawson KD, Kolbe-Alexander TL, et al. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. *The Lancet* 2016; 388: 1311–1324.

Short versus long-term blood storage

Previous studies have suggested that differences in duration of blood storage prior to transfusion does not cause a difference in outcome for high-risk patient populations. A randomised trial has been performed to see if duration of blood storage has an effect on mortality among a general population of hospital patients.

Patients across four hospitals who required blood transfusions were randomised (1:2) to groups receiving blood from either short-term storage (n=6936) or long-term storage (n=13 922). For logistical purposes, only patients with type A or O blood were included. The primary outcome was in-hospital mortality.

Mortality was observed in 9.1% of the short-term group and 8.7% in the long duration group.

There were no significant differences in mortality found between the two groups.

Standard practice of using the oldest available blood for transfusion does not result in a higher risk of mortality compared to the use of blood stored for a shorter time.

Heddle NM, Cook RJ, Arnold DM, et al. Effect of short-term vs. long-term blood storage on mortality after transfusion. *NEJM* 2016; 375: 1937–1945.