

Infection

Third vaccine for mumps outbreaks

Receipt of a third dose of the measles-mumps-rubella (MMR) vaccine has been shown to help combat mumps outbreaks. The study was conducted during an outbreak of mumps in students at the University of Iowa. Of the 2015-2016 academic year enrolment cohort (over 20,000 students), 259 were diagnosed with mumps. Before the outbreak, 98% of students had been given at least two doses of the MMR vaccine. A third dose was given to nearly 5000 students during the outbreak. Those given a third dose had a lower risk of mumps than those who had only received two doses (6.7 versus 14.5 cases per 1,000). The vaccine was also shown to wane over time as an increased risk of mumps was found in students who had received their second and final dose 13 years or more before the outbreak. A third dose of MMR vaccine may improve mumps outbreak control.

Cardemil CV, Dahl RM, James L, et al. Effectiveness of a third dose of MMR vaccine for mumps outbreak control. *NEJM* 2017; 377:947-956.

Long-acting antiretroviral injections

Two antiretroviral drugs are being investigated for efficacy as long-acting maintenance therapies for HIV-1 viral suppression. The two drugs, long-acting cabotegravir and rilpivirine, have been investigated for efficacy when combined in a randomised phase 2b, open label study. Treatment naïve HIV-1 positive adults were started on oral therapies (oral cabotegravir plus abacavir-lamivudine) once daily for a 20-week induction period and were then assigned to a regimen of either 4-weekly or 8-weekly cabotegravir plus rilpivirine intramuscular injections or continued daily oral therapies. Nearly 300 participants took part in the maintenance portion of the study following the induction period. Viral suppression at week 96 was maintained in 84% of participants receiving oral treatment, 87% in the 4-weekly group and 94% in the 8-weekly group. Two-drug injections of the long-acting antiretrovirals cabotegravir and rilpivirine given at either 4 or 8 week intervals were well tolerated and as efficacious in maintaining suppression of HIV viral load as daily oral therapy up to 96 weeks.

Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet* 2017; 390:1499-1510.

Candidate mRNA based vaccine for rabies

Preclinical models suggest that mRNA based vaccines are safe and immunogenic. A phase 1 study based in Germany has just reported its findings of a first-in-human proof-of-concept trial for a prophylactic mRNA-based vaccine encoding rabies glycoprotein (CV7201). Eligible volunteers were healthy adults, aged 18-40 years, with no prior rabies vaccination. Participants (n=101) received three doses of CV7201 either intradermally or intramuscularly by a needle-syringe or one of three needle-free devices. The primary endpoint was safety and tolerability of the vaccine and a further outcome was to establish the lowest dose of CV7201 that could neutralise the rabies virus (closest to the WHO-specified titre). When administered by needle-free device the immune response was favourable and met WHO-specified titres, however, it was shown to be ineffective with needle-syringe injection. Injection site reactions were reported in 94 and 97 per cent of intradermally and intramuscularly vaccinated participants and 10 grade 3 systemic adverse events were reported. Needle-free administration of this mRNA-based vaccine may be effective and against rabies and generally tolerable. The study continues for long-term safety and immunogenicity follow up.

Alberer M, Gnad-Vogt U, Hong HS, et al. and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. *Lancet* 2017; 390:1511-1520

Review of cholera vaccine efficacy

Cholera outbreaks hit resource-poor settings and can devastate the populations they touch. Killed whole-cell oral cholera vaccines (kOCVs) are emerging as standard management. However, studies on efficacy of kOCVs have produced varied results, presenting a challenge for public health policy makers. To better understand the effectiveness of kOCVs a group has conducted a meta-analysis and systemic review, aiming to linearise results and calculate average estimates of kOCV efficacy. Data were extrapolated from seven randomised trials and six observational studies, totalling information from 700 patients. Two-dose efficacy estimates showed that vaccine efficacy in children

was better in those five years old and over, compared to those under five. For all patients, two-dose efficacy estimates averaged 56% in the first year and 59% in the second year. However, the average efficacy decreased to 39% in year four. The cholera protective effect of two kOCV doses may last for up to 3 years, but wane after that. One dose may be protective at least in the short term, which could have important implications for management in an outbreak setting.

Bi Q, Ferreras E, Pezzoli L, et al. Protection against cholera from killed whole-cell oral cholera vaccines: a systematic review and meta-analysis. *Lancet Infectious Diseases* 2017; 17:1080-1088

Respiratory

Management for mild COPD

Chronic obstructive pulmonary disease (COPD) patients can suffer from a decreased lung function over time. Despite this, few mild sufferers receive medication due to presenting with few symptoms. A trial conducted in China has investigated if the use of tiotropium, a long-acting anticholinergic bronchodilator given to improve airflow and COPD symptoms, may benefit those with mild COPD and ameliorate the decline in forced expiratory volume in 1 second (FEV1) results that occurs with decreased lung function over time. Participants were of COPD Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 (mild) or stage 2 (moderate) severity. Participants were randomised to receive either tiotropium (n=388) or placebo (n=383) once daily for two years. At 24 months, the patients who had received tiotropium had a significantly higher FEV1 than those given placebo. The annual decline in FEV1 was significantly less versus placebo in the tiotropium group after bronchodilator use but not before bronchodilator use. Early-stage COPD of GOLD stage 1 or 2 patients may benefit from the use of daily tiotropium to help prevent declining FEV1.

Zhou Y, Zhong N, Li X, et al. Tiotropium in early-stage chronic obstructive pulmonary disease. *NEJM* 2017; 377:923-935.

Add-on therapy for uncontrolled asthma

It is estimated that over 50 million people suffer from mild-to-severe uncontrolled asthma, globally. These patients often experience quality-of-life reducing exacerbations that require medical help, despite being on maintenance therapies. One study has set out to investigate if asthma

might better be controlled with the use of add-on macrolide antibiotic therapy to patients on concurrent maintenance treatment of inhaled corticosteroid and long-acting bronchodilator. Participants on the above maintenance therapy were randomly assigned to receive either additional oral azithromycin (n=213) or placebo (n=207) three times a week up to 48 weeks. By the end of the trial the treatment group given Azithromycin experienced a significantly lower rate of asthma exacerbations and an improved asthma-related quality of life compared to the placebo group. It was also found that diarrhoea was significantly more common in azithromycin receiving patients versus placebo. Oral azithromycin given to mild-to-severe uncontrolled asthmatics as an add-on therapy to maintenance treatment can help improve symptoms.

Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017; 390: 659-668

Biomarker for COPD progression

Respiratory airway mucins are implicated in the poor transport of mucus seen in sufferers of COPD. The use of respiratory airway mucin concentration as a biomarker of COPD has been investigated. It was theorised that high mucin concentrations may be implicated in the disease progression of chronic bronchitis, a feature of COPD sufferers. The study looked at total mucin concentrations in over 900 COPD sufferers. Mucin concentrations were highest in severe COPD participants who were current or former smokers versus controls with no history of smoking and were higher again in participants with a history of two or more COPD exacerbations per year. The researchers concluded that airway mucin concentration could be a potential candidate for a diagnostic biomarker and therapeutic target of chronic bronchitis in COPD sufferers.

Kesimer M, Ford AA, Ceppe A, et al. Airway mucin concentration as a marker of chronic bronchitis. *NEJM* 2017; 377:911-922.

Chronic cough in idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a progressive condition that critically reduces length of life. Eighty percent of those with IPF suffer from a debilitating cough that is not often responsive to medical therapies. A phase 2 trial has investigated the safety and efficacy of nebuliser-administered PA101, a formula-

tion of sodium cromoglicate. Two patient groups were included, IPF patients with chronic cough (n=24) and patients with chronic idiopathic cough (CIC) (n=27). The randomised, double-blind, placebo-controlled trial ran in centres across the UK and the Netherlands. Participants were given 3 doses of drug or placebo via oral inhalation for 2 weeks, followed by a 2 week wash out period and then 2 weeks of treatment in the opposite arm of the study. In patients with IPF, PA101 was effective in reducing frequency of daytime coughing by 31% compared to placebo. However, PA101 was not effective in CIC. The therapy was well tolerated among both patient groups. The researchers suggested that PA101 may work against coughs in an IPF-disease specific manner, warranting further investigation.

Birring SS, Wijsenbeek MS, Agrawal S, et al. A novel formulation of inhaled sodium cromoglicate (PA101) in idiopathic pulmonary fibrosis and chronic cough: a randomised, double-blind, proof-of-concept, phase 2 trial. *Lancet Resp Med* 2017; 5:806-815

Obs & Gynae

Post-caesarean infection in obese women

As the incidence of obesity rises it is becoming increasingly important for medical practice to adapt in order to minimise the risks associated with obesity. Obese women are known to have an increased risk of post-caesarean surgical site infection (SSI). A group of researchers in Ohio, USA have investigated whether the use of prophylactic postpartum antibiotics, given with usual preoperative cephalosporin prophylaxis helps combat SSI incidence in obese women following caesarean delivery. In this double-blind trial 403 participants were randomly assigned to receive standard preoperative antibiotic prophylaxis of cephalosporin and either oral cephalexin and metronidazole (n=202) or placebo (n=201) every 8 hours for 48 hours following caesarean delivery. At 30 days' post caesarean, the rate of SSI in the postpartum antibiotic group was 6% compared to 15% in the women given placebo. No serious adverse events were reported in either group. Standard preoperative antibiotic prophylaxis may be more effective when combined with 48-hours of postoperative oral cephalexin and metronidazole for protection against surgical site infection in obese women undergoing caesarean.

Valent AM, DeArmond C, Houston JM, et al. Effect

of post-caesarean delivery oral cephalexin and metronidazole on surgical site infection among obese women: A randomized clinical trial. *JAMA* 2017;318(11):1026-1034. doi:10.1001/jama.2017.10567

Breastfeeding and endometriosis

Endometriosis is a chronic disorder that can place a huge burden on the wellbeing of those affected. It is theorised that breastfeeding may be protective against endometriosis due to the low oestrogen environment. Otherwise, oestrogen presence can stimulate maintenance and growth of endometriosis lesions. A prospective cohort study set out to investigate this possible link in a study involving over 7,000 women with a history of one or more pregnancies. Breast feeding duration total, exclusive breast feeding, and postpartum amenorrhea were reported. The main outcome of the study was laparoscopically confirmed endometriosis. Women who reported a total lifetime duration of breastfeeding at less than one month were found to have an incidence of endometriosis at 453 cases per 100,000 person years versus 184 cases per 100,000 when breastfeeding for a lifetime total of ≥ 36 months. Duration of total and exclusive breastfeeding were significantly associated with a decreased risk of endometriosis. It is likely this link is due to postpartum amenorrhea and other factors. This highlights a potentially beneficial modifiable behaviour for pregnant women that could moderate risk for endometriosis.

Farland LV, Eliassen AH, Tamimi RM, et al. History of breast feeding and risk of incident endometriosis: prospective cohort study. *BMJ* 2017; 358 :j3778

Interventions for gestational weight gain

Obesity and excessive weight gain in pregnancy can have negative outcomes for mother and child, both during pregnancy and in later life. This is emerging as a real problem, especially when considering that estimates predict half of all women of childbearing age are overweight or obese. A systematic review and meta-analysis has been conducted to assess effects of dietary and physical interventions on pregnancy outcomes, in particular, gestational weight gain and maternal and offspring outcomes. Data from over 12,500 women from 36 randomised trials was included in the analysis. Intervention groups did result in a lower gestational weight gain than control groups. The study could not find a significant reduction in odds of adverse neonatal and maternal outcomes with diet and physical based

interventions. Data from 32 of the studies showed strong evidence supporting the effect of interventions in reducing the odds of pregnant woman needing a caesarean section for delivery. Dietary and physical interventions during pregnancy can help reduce weight gain in pregnancy.

International Weight Management in Pregnancy (i-WIP) Collaborative Group. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. *BMJ* 2017; 358 :j3119

Postpartum depression

One of the most common postnatal complications is postpartum depression (PPD), affecting 5-15% of all women following childbirth. There are long term impacts of PPD that can influence both the mother's risk of long term depression and the child's development. A research group has carried out a study to estimate the incidence of postpartum affective disorder (AD), duration of treatment, and rate of subsequent postpartum AD in women with no prior psychiatric history. The study was conducted using a cohort of women taken from Danish national registers and included over 457,000 women who prior to their firstborn child had no psychiatric medication or hospital contact history. Postpartum AD occurred with 0.6% of births. For those women affected, 28% of women were still on treatment one year after treatment initiation and 5% at 4 years. Women with PPD and psychiatric hospital contact following their first birth had a 46 times higher rate of a recurrent episode following a second birth, and those who were given antidepressants for PPD had a 26 times higher rate than women with no postpartum AD history. Rasmussen M-LH, Strøm M, Wohlfahrt J, et al. (2017) Risk, treatment duration, and recurrence risk of postpartum affective disorder in women with no prior psychiatric history: A population-based cohort study. *PLoS Med* 14(9): e1002392. <https://doi.org/10.1371/journal.pmed.1002392>

Pregnancy outcomes with dengue

Dengue is a mosquito transmitted disease with a high morbidity, mortality and economic burden. Over recent years it has had a huge impact on Brazil with over 5,000 deaths since 2002. There are increasing rates of infection among infant, elderly and pregnant groups. However, few studies have monitored the impact of dengue in pregnancy on foetal outcomes. With this in mind, a group has looked at birth outcomes among pregnant women

in Brazil who had a symptomatic dengue infection during pregnancy between 2007 and 2013 via a retrospective observational cohort study. Data were taken from 3,898 dengue-positive women, 3,100 dengue-negative women, and 3,800 newborn babies (taken from a reference population). Birthweight did not seem to differ between groups. Across all groups, the prevalence of congenital malformations was lower than one percent. After adjusting for cofounders, analysis showed that risk of preterm birth was higher in women who were positive for dengue versus the non-dengue group.

Nascimento LB, Siqueira CM, Coelho GE, et al. Symptomatic dengue infection during pregnancy and livebirth outcomes in Brazil, 2007–13: a retrospective observational cohort study. *Lancet Infectious Diseases* 2017. 17:949-956.

Paediatrics

Biomarker for antibiotic therapy guidance

In high income countries, the prevalence of early-onset sepsis in late-preterm and term neonates is confirmed, at most, in 0.1% of infants. Despite this, up to 7% of infants are given antibiotics for suspected early-onset sepsis in the first three days of life. Procalcitonin is one of the most competent biomarkers of severe bacterial infections in neonates. A randomised trial conducted across Dutch, Swiss, Canadian and Czech hospitals has investigated if the use of a procalcitonin-guided decision making strategy could help reduce the frequency and duration at which such neonates are given antibiotics. Over 1,700 eligible neonates were enrolled in the study and randomised to receive either procalcitonin-guided therapy (n=866) or standard therapy (n=844). Duration of antibiotic therapy was significantly reduced in the group whose care was guided by procalcitonin. Further outcomes of non-inferiority for re-infection or death could not be assessed due to the low occurrence and absence of these, respectively. For infants with suspected early-onset sepsis a procalcitonin-guided decision making approach was superior to the standard care in reducing potentially unnecessary antibiotic therapy.

Stocker M, van Herk W, el Helou Salhab, et al. Procalcitonin-guided decision making for duration of antibiotic therapy in neonates with suspected early-onset sepsis: a multicentre, randomised controlled trial (NeoPlns). *Lancet* 2017; 390:871-881

Childhood inflammatory bowel disease and cancer

It is well-documented that inflammatory bowel disease (IBD) is a risk factor for the development of cancers, particularly gastrointestinal. However, much of the research that has informed us on this area has been conducted using patients with adult-onset IBD. There is an increasing prevalence of paediatric Crohn's, this combined with the fact that there have been changes to bowel disease management over the years, warrants further investigation into the prevalence and impact of childhood-onset IBD. Data were taken from a Swedish national patient register and 9405 cases of childhood onset IBD (<18 years) were included and matched to over 92,000 comparators. After an average follow-up of 27 years, 3.3 per 1,000 person years with childhood-onset IBD developed primary cancers, compared to 1.5 per 1000 person years in the matched controls. Those with childhood-onset ulcerative colitis and Crohn's disease had hazard ratios of 2.6 and 1.7, respectively, for any cancer. The relative risk for gastrointestinal cancers for those with IBD was 1.8. The risk of cancer following childhood-onset IBD has not declined over time.

Olén O, Askling J, Sachs MC, Frumentio P, Neovius M, Smedby KE et al. Childhood onset inflammatory bowel disease and risk of cancer: a Swedish nationwide cohort study 1964-2014. *BMJ* 2017; 358 :j3951

Acute kidney injury

Combination antibiotic therapy is a common management strategy for hospitalised children when battling serious infection. For adults, combination therapy of intravenous (IV) vancomycin plus piperacillin sodium/tazobactam sodium is associated with a higher risk of acute kidney injury (AKI) versus combination therapy of vancomycin plus one other β -lactam antibiotic. Researchers now want to establish if this combination is safe in children by investigating the risk of AKI. The retrospective cohort study included children aged between 6 months and 18 years (n=1915) given IV vancomycin plus one other antipseudomonal β -lactam combination therapy during a hospitalisation period of 3 or more days. The particular combination of IV vancomycin plus piperacillin/tazobactam was associated with higher odds of children developing AKI versus vancomycin plus one other antipseudomonal β -lactam combination. Vancomycin combination therapy with piperacillin/tazobactam, given intravenously, may increase risk of acute kidney injury in hospitalised children. The researchers recommend that paediatricians be cautious

when considering combination therapies in hospitalised children.

Downes KJ, Cowden C, Laskin BL, et al. Association of acute kidney injury with concomitant vancomycin and piperacillin/tazobactam treatment among hospitalized children. *JAMA Pediatr.* 2017. doi:10.1001/jamapediatrics.2017.3219

Increasing fat-free tissue in malnourished children

Children from low-income countries have high rates of moderate acute malnutrition (MAM) which can lead to morbidity and death. It is imperative that optimum management strategies are investigated to help improve the health of the millions of children with MAM to prevent the adverse downstream outcomes. And indeed, further research on food supplements has been recommended by the World Health Organisation. Currently, lipid-nutrient supplement (LNS) and corn-soy blends (CSB) are both of intrigue but there is some concern that LNS may cause accumulation of fat tissue. Previous studies have focused on total weight gain, not composition of weight gain, which can impact a child's health if too fatty. A large trial included over 1,500 children with MAM in Burkina Faso, West Africa. The study investigated effectiveness of supplemental foods, using measurements of body composition to assess weight gain and fat-free tissue. The study found that fat-free tissue was best increased using LNS based supplement compared to CSB supplements. The researchers support wider use of LNS to help manage children with moderate acute malnutrition.

Fabiansen C, Yaméogo CW, Luel-Brockdorf A-S, et al. Effectiveness of food supplements in increasing fat-free tissue accretion in children with moderate acute malnutrition: A randomised 2 × 2 × 3 factorial trial in Burkina Faso. *PLoS Med* 2017; 14(9): e1002387.

and those who did not seek or receive surgery. The mean weight change at 12 years follow up was -35 kg for the surgical group and -2.9 and 0 kg weight change for the two non-surgical groups. At two years, 75% of the surgery patients who had type 2 diabetes at baseline had remitted (66 of 88 patients), with 51% still in remission at 12 years. For both hypertension and dyslipidaemias, the surgery group had a significantly lower incidence than the non-surgery patients. Weight loss and improved metabolic profiles may be durable following Roux-en-Y gastric bypass surgery.

Adams TD, Davidson LE, Litwin SE, et al. Weight and metabolic outcomes 12 years after gastric bypass. *NEJM* 2017; 377:1143-1155.

Conservative breast radiotherapy

Patients who have undergone radiotherapy for early-stage breast cancer may have a reduced risk of recurrence by up to 50%. The standard for practice in the United Kingdom is to use whole breast radiotherapy. However, there is a group of thought that more conservative radiotherapy may still be able to produce the same outcomes regarding local recurrence but with fewer adverse effects. A multicentre trial was conducted across 30 radiotherapy sites in the UK involving women who had breast conserving surgery for unifocal early breast cancer. Three groups included participants who were given whole breast radiotherapy (control n=674), reduced-dose whole-breast radiotherapy (n=673), and partial-breast radiotherapy (n=669) for 15 daily treatment fractions. Primary endpoint was ipsilateral local relapse. At 5 years follow up both the reduced-dose and partial-breast radiotherapy were considered non-inferior to standard whole breast radiotherapy with regards to the primary endpoint. Adverse tissue events were similar or lower in the partial and reduced settings. Conservative radiotherapy to the breast for patients with excised, early stage breast cancer may be considered as a reasonable treatment option.

Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet* 2017; 390:1048-1060

Dental procedures and infective endocarditis

Some evidence suggests a link between invasive dental procedures and the development of infective endocarditis,

due to oral streptococci, specifically, in those with prosthetic heart valves. This link is being investigated further following questions raised regarding the use of antibiotic prophylaxis prior to invasive dental procedures. A cohort of over 138,800 adults with prosthetic heart valves living in France were included in the study. Over 100,000 invasive dental procedures were performed between them, 50% of which received antibiotic prophylaxis. After an average follow up of 1.7 years, 267 individuals developed an infective endocarditis that was associated with oral streptococci. There was no significant increased rate of such endocarditis following periods exposed to an invasive dental procedure, and after a procedure given without prophylactic antibiotics, compared to non-exposure. However, following a crossover analysis, it was found that invasive dental procedure exposure was more frequent in a period of 3 months immediately preceding oral streptococcal infective endocarditis, than in the matched control period. The development of infective endocarditis may be influenced by invasive dental procedures in adults with prosthetic heart valves.

Tubiana S, Blotière PO, Hoen B, et al. Dental procedures, antibiotic prophylaxis, and endocarditis among people with prosthetic heart valves: nationwide population based cohort and a case crossover study *BMJ* 2017; 358 :j3776

Miscellaneous

Durability of bariatric surgery benefits

Positive short term outcomes for those who have received bariatric surgery are well documented, including improved metabolic profiles for conditions such as type 2 diabetes. A study has set out to assess the long-term impact of bariatric surgery on patient's health at 12 years' post-surgery. Over 1,000 patients with severe obesity were included in the study, 418 of which had undergone Roux-en-Y gastric bypass surgery. The remainder of patients were split into two groups, those who sought but did not receive surgery,