Infection

Safety and tolerability of Chikungunya vaccine

Chikungunya is an endemic disease in Africa and south Asia. The disease has no vaccine or drug for preventing or treating the infection.

A recent phase 1, open label clinical trial evaluated the safety of a Chikungunya vaccine (VRC-CHKVLP059-00-VP).

Participants aged 18-50, were assigned to sequential dose level groups of 10µg, 20µg or 40µg. Participants received doses on weeks 0, 4 and 20, with a follow-up of 44 weeks after enrolment.

Of the 25 participants that started, only 2 dropped out, which was not to do with any adverse side effects. The vaccinations were well tolerated and no serious adverse event reported.

Neutralising antibodies were detected in all groups by the third injection, with these antibody responses increasing after the third injection in all groups.

With the vaccine being well tolerated, safe and immunogenic; further studies are now required.

Chang J, Dowd A, Mendoza H, et al. Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial. *Lancet* 2014; S0140-6736(14): 61185-5.

The effect of meningococcal carriage in university students receiving vaccinations

The carriage rates of meningococcal in 18-24 year olds was recently assessed with the use of quadrivalent glycoconjugate (MenACWY-CRM) and serogroup B (4CMenB) vaccines. Over 2000 students were randomised to have either a single dose of MenACWY-CRM, or two doses of 4CMenB one month apart, or placebo.

Oropharyngeal swabs were taken 6 times over 12 months, with the first occurring on day one of the study. The primary outcome of the study was the carriage rates 1 month after completing each treatment regime.

By the first month, there were no significant difference in carriage rates between the control group and vaccine groups. However, both vaccines significantly reduced meningococcal carriage rates 12 months after vaccination, which might mean transmission could be affected with widespread vaccination implementation.

Read C, Baxter D, Chadwick R, et al. Effect of a quadrivalent meningococcal ACWY glycoconjugate or a serogroup B meningococcal vaccine on meningococcal carriage: an observer-blind, phase 3 randomised clinical trial. *Lancet* 2014; 384: 2123–2131.

The efficacy of dengue vaccine

Even with vector-control, the rate of dengue infections are increasing, which has lead to development of a number of dengue vaccines.

A phase 3 trial of a tetravalent dengue vaccine assessed the efficacy of the vaccine against symptomatic, virologically confirmed dengue (VCD) infection more than a month after the third injection. Over 20 000 children from countries where the incidence of dengue is high were randomly assigned to have three injections of a recombinant, live, attenuated tetravalent dengue vaccine or placebo at 0, 6 and 12 months. Patients and investigators were blinded to what treatment was given.

After 28 days from the third injection, 176 cases of VCD and 221 VCD cases were reported in the vaccine and placebo group respectively, which gives the vaccine efficacy of 60.8%. Vaccine efficacy against hospitalisation was 80.3%.

The Safety and Immunogenicity of Recombinant, Live Attenuated Tetravalent Dengue Vaccine (CYD- TDV) was found to be efficacious against dengue infection, while having the same safety profile as placebo.

Villar L, Dayan G, Arredondo-García J, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. *NEJM* 2014; 10.1056/NEJMoa1411037.

Dermatology

New treatment for ACE-inhibitor induced angioedema

One third of angioedema is caused by angiotensin-converting-enzyme (ACE) inhibitors. Frequently, angioedema manifests itself in the upper airway which can result in laryngeal obstruction and death. Currently, there is no approved treatment for this but standard therapy consists of prednisolone and clemastine. A recent randomised trial has assessed the efficacy of subcutaneous icatibant (a bradykinin β2 antagonist) at treating ACE-inhibitor-induced angioedema. The primary endpoint measured time to oedema resolution.

The median time to complete resolution in the icatibant group (n=13) was 8 hours – significantly shorter than the 27.1 hours observed among patients randomised to the standard treatment (n=14). Further analysis demonstrated more patients in the icatibant group had resolution within 4 hours and had a shortened time to symptom relief compared with the standard treatment.

When treating ACE-inhibitor-induced angioedema, icatibant reduced the time to resolution in comparison to treatment with a glucocorticoid and an antihistamine.

Baş M, Greve J, Stelter K. A Randomized Trial of Icatibant in ACE-Inhibitor–Induced Angioedema. *NEJM* 2015; 372: 418–25.

Treating psoriasis with ponesimod

Psoriasis is a T-cell mediated chronic inflammatory condition. Therefore, decreasing circulating T-cell numbers with ponesimod is a potential treatment.

Therefore, a study published results on the effect of ponesimod for psoriasis treatment. A total of 326 participants divided into three groups received 20mg or 40mg of ponesimod or placebo once daily for 16 weeks.

By 16 weeks a reduction in disease activity was achieved in 46.0%, 48.1% and 13.4% of participants in the 20mg, 40mg and placebo groups respectively.

Ponesimod treated patients were then re-randomised for maintenance dose with ponesimod or placebo. By 28 weeks 71.4% and 77.4% of participants receiving 20 mg or 40 mg of ponesimod achieved a reduction in their disease activity scores. Roughly 40% of those receiving the placebo showed a decrease in disease activity at 28 weeks. However, the drug was associated with dyspnoea, raised liver enzymes and dizziness.

Ponesimod showed a significant clinical benefit by 16 weeks, which increased with maintenance therapy.

Vaclavkova A, Chimenti S, Arenberger P, et al. Oral ponesimod in patients with chronic plaque psoriasis: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet* 2014; 384: 2036–2045.

Obs & Gyn

Labour induction with prostaglandins

The number of labour inductions have increased over the past two decades. Although prostaglandins remain a preferred method for induction of labour, current recommendations for their usage have not been based on an overview of evidence.

Therefore, a recent systematic review and meta-analysis using 260 studies (incorporating 48 068 women) has quantified the effectiveness and safety of different prostaglandins for labour induction.

The results found that vaginal

misoprostol (≥50 µg) had the highest probability of achieving vaginal delivery within 24 hours, whereas oral misoprostol had the lowest probability of caesarean section.

Misoprostol may be the best prostaglandin for labour induction.

Alfirevic Z, Keeney E, Dowswell T, et al. Labour induction with prostaglandins: a systematic review and network meta-analysis. *BMJ* 2015; 350: 217.

The burden of tuberculosis in pregnancy

Research predicts 28% of maternal deaths are due to non-obstetric causes such as infection. In 2013, 3.3 million cases of tuberculosis (TB) were estimated to occur globally in women. TB in pregnancy is associated with poor outcomes for both the neonate and the mother. Therefore, a recent study aimed to quantify the burden of TB disease among pregnant women.

Estimates were calculated using data on population, birth rates, and active TB cases from 217 countries. Furthermore, the study aimed to establish how maternal care services could improve case detection among pregnant women.

It was estimated that 216 500 active TB cases existed in pregnant women globally in 2011, with the greatest burden were in Africa (89 400 cases). Clinical radiography or Xpert RIF/MTB delivered through maternal care services could detect as many as 114 000 and 120 000 cases respectively.

The burden of TB in pregnancy is substantial.

Sugarman J, Colvin C, Moran A, et al. Tuberculosis in pregnancy: an estimate of the global burden of disease. *Lancet Global Health* 2014; 2: 710–6.

Pre-exposure HIV prophylaxis for women

Women of reproductive age need effective interventions to prevent HIV infection. Therefore a number of different prophylactic drugs have been developed.

A recent randomised trial among sub-Saharan African women assessed the efficacy of three different daily prophylaxis regimens. A total of 5029 women were randomised to receive either oral tenofovir disoproxil fumarate (TDF), oral tenofovir-emtricitabine (TDF-FTC), 1% tenofovir (TFV) vaginal gel, or placebo (oral or vaginal gel). The primary end point was HIV infection.

Over the study period, a total of 312 HIV infections occurred. However, no significant differences were observed between the three regimens and the corresponding placebo groups. Plasma samples obtained from participants showed adherence to the study drugs was low.

None of the three HIV prophylaxis drug regimens reduced the rates of HIV acquisition.

Marrazzo J, Ramjee G, Richardson B, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. *NEJM* 2015; 372: 509–18.

Paediatrics

Isotonic versus hypotonic intravenous fluids for children

The appropriate sodium concentration of intravenous fluid used to maintain hydration among children in hospital is controversial. The use of hypotonic intravenous fluid has been associated with hyponatraemia, which can result in neurological morbidity and mortality. Therefore, some have suggested the use of isotonic fluid for rehydration which may reduce the risk of hyponatraemia.

A recent randomised trial has assessed the occurrence of hyponatraemia among 690 children receiving rehydration therapy with either intravenous fluids containing 140 mmol/L of sodium (Na140) or 77 mmol/L of sodium (Na77).

Significantly fewer patients given Na140 developed hyponatraemias compared with those given Na77 (12 patients (4%) vs 35 (11%), respectively; odds ratio, 0.31). No cerebral oedema occurred in either group. One patient in the Na140 group had seizures compared with seven who received Na77.

Isotonic intravenous fluids (sodium concentration, 140mmol/L) had a lower risk of hyponatraemia.

McNab S, Duke T, South M, et al. 140 mmol/L of sodium versus 77 mmol/L of sodium in maintenance intravenous fluid therapy for children in hospital (PIMS): a randomised controlled double-blind trial. *Lancet* 2014; S0140-6736(14): 61459-8.

Long-acting reversible contraception and teenage pregnancy

Teenage pregnancy is associated with negative health and social consequences borne by teenage mothers and their children, but there is also a substantial national financial burden. A project was conducted in the United States to promote long-acting, reversible contraception (LARC) in order to reduce unintended pregnancy among teenagers.

The project entailed enrolling and educating 1400 teenagers (aged 14-19) about contraception, with an emphasis on LARC. The participants were then provided with reversible contraception at no cost and followed-up over 2-3 years.

A total of 72% of girls chose an intrauterine device or implant (LARC contraceptive methods). During the 2008-2013 period, the mean annual rates of pregnancy, birth and abortion among participants were 34.0, 19.4, and 9.7 per 1000 teens respectively. By comparison, the U.S. averages in 2008 for pregnancy, birth, and abortion were 158.5, 94.0, and 41.5 per 1000 respectively.

LARC provided for teenage girls at no cost resulted in rates of pregnancy, birth, and abortion being significantly lower than the national rates.

Secura G, Madden T, McNicholas C, et al. Provision of No-Cost, Long-Acting Contraception and Teenage Pregnancy. *NEJM* 2014; 371: 1316–23.

Maternal micronutrient and iron-folic acid supplementation

Micronutrient deficiencies during pregnancy may be associated with adverse effects on foetal and infant health. The evidence of such effects is insufficient to guide antenatal micronutrient supplementation.

A cluster randomised, double masked trial studied outcomes in infants whose mothers were given either a supplement containing 15 micronutrients or a single iron-folic acid supplement. Supplements were to be taken daily from early pregnancy up to 12 weeks postpartum.

The primary outcome was all-cause mortality at 6 months. The multiple micronutrient supplements were not found to significantly reduce infant mortality in comparison to the iron-folic acid group (741 versus 764 deaths respectively).

The results from the study showed that there was no statistically significant reduction in stillbirths between the groups based on the nutritional supplement they were taking.

West K, Shamim A, Mehra S, et al. Effect of Maternal Multiple Micronutrient vs Iron–Folic Acid Supplementation on Infant Mortality and Adverse Birth Outcomes in Rural Bangladesh: The JiVitA-3 Randomized Trial. *JAMA* 2014; 312: 2649–2658.

Respiratory

Adjunct prednisolone for community-acquired pneumonia

Research has produced conflicting data about the benefit of adding systemic corticosteroids to standard treatment of community-acquired pneumonia (CAP). A recent double-blinded randomised trial aimed to assess whether short-term corticosteroid treatment reduces the time to clinical stability (defined as

stable vital signs).

A total of 785 patients suffering with CAP (presenting within 24 hours) were randomly assigned to receive standard care plus prednisone (50 mg daily) for 7 days or placebo.

Analysis revealed median time to clinical stability was 3 days for the prednisone group compared with 4.4 days in the placebo group – yielding a significant hazard ratio (HR) of 1.33. Although pneumonia-associated complications up to day 30 did not differ between the groups, the prednisone group had a higher incidence of hyperglycaemia requiring treatment.

In patients with CAP, adjunct prednisone treatment for 7 days shortened time to clinical stability.

Blum C, Nigro N, Briel M, et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2015; S0140-6736(14)62391-6.

Thoracic radiotherapy for extensive lung cancer

Persistent intra-thoracic disease in patients with extensive stage small-cell lung cancer (ES-SCLC) is a common issue in those undergoing chemotherapy and prophylactic cranial irradiation.

A recent trial assessed 1 year survival in 495 patients with ES-SCLC who underwent thoracic radiotherapy. All patients had previously undergone chemotherapy and prophylactic cranial irradiation. Patients were randomised into either having the thoracic radiotherapy (30gy in ten fractions) or having no radiotherapy.

Overall survival between groups was not significantly different at 1 year. In the secondary analysis, 2-year overall survival was significantly higher in the radiotherapy group (13% vs 3%).

Progression was less likely to occur in the radiotherapy group at 6 months. No severe toxic effects were recorded, but the most common side effects were fatigue and dyspnoea.

The findings of this trial concluded that thoracic radiotherapy should be considered in all patients with ES-SCLC who respond to chemotherapy.

Slotman B, Tinteren H, Praag J, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet* 2015; 385: 36–42.

Smoking cessation: cytisine versus nicotine

Cytisine has been available for smoking cessation in Europe since the 1960s. Past placebo-controlled trials have shown cytisine nearly double the chances of smoking cessation at 6 months.

A study evaluated whether cytisine was as effective as nicotine-replacement therapy (NRT). Adult smokers looking to quit smoking were recruited into this open label non-inferiority trial.

Participants were randomised for 25 days of cytisine or NRT for 2 months. Primary outcomes were self-reported continuous abstinence at 1 month.

After 1 month, 40% and 31% of participants in the cytisine and NRT groups respectively reported continuous smoking abstinence. Cytisine was superior for continuous abstinence in comparison to NRT. In subgroup analysis, cytisine was superior in women and inferior in men when compared to NRT. Cytisine treatment was associated with higher frequency of side effects such as nausea and sleep disturbances.

It was concluded that with brief behavioural support, cytisine was superior to NRT for smoking cessation.

Walker N, Howe C, Glover M, et al. Cytisine versus Nicotine for Smoking Cessation. *NEJM* 2014; 371: 25; 2353–2362.

Diabetes

Glucagon-like-peptide 1 agonists and insulin combination treatment for type 2 diabetes

Glucagon-like-peptide 1 (GLP-1) agonists are injectable drugs that improve glycaemic control and weight loss. Glycaemic control in type 2 diabetes with hypoglycaemics can lead to side effects such as hypoglycaemia and weight gain. It has been postulated that combining insulin with GLP-1 agonists will lead to better glycaemic control and attenuation of side effects.

Fifteen randomised control trials assessed the effects of combination treatment with GLP-1 and insulin in type 2 diabetics.

Combination treatment led to an improved mean reduction in HBA1C of -0.44% (95% CI -0.6, -0.29) and improving the likelihood of achieving a HBA1C of 7% (RR 1.92, CI 1.43, 2.56). Combination treatment also lead to a mean weight reduction of -3.22kg (-4.90 to -1.54).

The analysis concluded that a GLP-1 agonist and basal insulin combination treatment achieved ideal glycaemic control with no increased weight gain or hypoglycaemic events.

Eng C, Kramer K, Zinman B, et al. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet* 2014; 384: 2228–34.

Incidence of diabetes after bariatric surgery

Bariatric surgical interventions for obesity have been associated with improved outcomes such as weight loss and decreased morbidity. However, the effects of bariatric surgery on the development of diabetes in obese people has not been well defined.

A matched cohort study aimed to quantify the effect of bariatric surgery on the development of type 2 diabetes among an obese population.

A total of 2167 patients who had undergone bariatric surgery were matched one-to-one for BMI, age, sex, and HbA1c with controls who had not undergone surgery. The primary outcome was the development of diabetes.

After a follow-up of 7 years, 38 new diagnoses of diabetes were made in the surgery patients compared with 177 in the controls. The incidence of diabetes diagnosis was 28.2 per 1000 person-years in the controls and 5.7 per 1000 person-years in bariatric surgery patients (significant hazard ratios, 0.20).

Bariatric surgery in obese people is associated with a reduced incidence of clinical diabetes.

Booth H, Khan O, Prevost T, et al. Incidence of type 2 diabetes after bariatric surgery: population-based matched cohort study. *Lancet Diabetes Endocrinology* 2014; 2: 963–8.

Critical care

Severe trauma, transfusions, and blood products ratios

Early transfusions with higher ratios of blood products (plasma, platelets and red blood cells) have been associated with improved outcomes among patients experiencing haemorrhagic shock. However, the efficacy of transfusing patients with major bleeding using plasma, platelets and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio has remained unestablished.

The Pragmatic Randomised Optimal Platelet and Plasma Ratios (PROPPR) trial randomised severely injured patients requiring massive transfusion to receive blood products in a ratio of either 1:1:1 (n=338) or 1:1:2 (n=342) during resuscitation. The primary outcomes measured 24-hour and 30-day mortality.

No significant differences were detected in mortality at 24 hours (12.7% in 1:1:1 group vs 17.0% in

1:1:2 group) or at 30 days (22.4% vs 26.1% respectively). However, patients receiving the 1:1:1 transfusion had significantly reduced rates of exsanguination and increased rates of haemostasis.

Mortality rates did not differ between patients receiving a massive blood transfusion of plasma, platelets, and red blood cells in a 1:1:1 or a 1:1:2 ratio.

Holcomb J, Tilley B, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA* 2015; 313: 471–82.

Effect different feeding regimes on outcomes in acute pancreatitis

Nasoenteric feeding is often used early on with severe acute pancreatitis to prevent gastrointestinal-derived infections. Evidence for such practice is limited, but a recent multicentre, randomised trial compared early nasoenteric feeding with oral feeding after presentation of acute pancreatitis.

Over 200 patients were randomly assigned to have nasoenteric feeding 24 hours after diagnosis or oral feeding 3 days after diagnosis. If the oral feeding was not tolerated then tube feeding was used instead. Primary endpoints of the study were the number of major infections or death during a 6 month follow-up.

The rate of major infections was 25% and 26% in the nasoenteral feeding and oral feeding respectively. The number of deaths between the groups was 11% and 7% respectively. The oral feeding was tolerated by 69% of patients.

The trial deemed there was no significant difference between the two different feeding regimes or superiority of nasoenteric feeding.

Bakker O, van Brunschot S, van Santvoort H, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *NEJM* 2014; 371: 1983–1993.

Efficacy of progesterone for traumatic brain injury

Along with the mortality and morbidity associated with traumatic brain injury (TBI), the condition has high financial costs to health services. Progesterones have been shown to have clinical neuroprotective benefits in randomised control trials.

A trial investigated the efficacy of progesterone for TBI. A total of 1195 patients were randomly assigned progesterone or placebo treatment. Patients included in the trial had severe TBI, with a Glasgow Coma Scale (GCS) of 8 or less.

Patients were given progesterone within 8 hours of injury and continued for 5 days. Primary efficacy endpoints were GCS scores 6 months after injury.

The percentage of patients with favourable outcomes at 6 months (defined as good recovery or moderate disability) were 50.4% and 50.5% in the progesterone and placebo groups respectively. Mortality and safety was similar between each groups.

This trial showed no clinical benefit for using progesterone in severe TBI.

Skolnick B, Maas A, Narayan R, et al. A clinical trial of progesterone for severe traumatic brain injury. *NEJM* 2014; 371: 2467–2476.

Misc

Latanoprost for open-angle glaucoma

Treatments for open-angle glaucoma aim to prevent vision loss through lowering intraocular pressure. However, no placebo-controlled trials have assessed the preservation of visual function. Therefore, a multicentre randomised placebo-controlled trial assessed the effects of latanoprost (a prostaglandin analogue) on vision preservation.

The study enrolled newly diagnosed patients across 10 centres. Participants were then assigned to receive latanoprost (n=231) or placebo (n=230) eye drops (once a day in both eyes). The primary endpoint was time to visual deterioration within 24 months.

At 24 months, mean reduction in intraocular pressure was 3.8 mmHg in the latanoprost group compared with 0.9 mmHg in the placebo group. Visual field preservation was significantly longer in the latanoprost group than in the placebo group (hazard ratio, 0.44). No serious adverse drug effects were recorded.

In patients with open-angle glaucoma, visual field function was significantly prolonged with the use of latanoprost eye drops.

Garway-Heath D, Crabb D, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet* 2014; S0140-6736(14): 62111-5.

Slotman B., van Tinteren H, Praag J, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet* 2014; S0140-6736(14): 61085-0.

The effects of handoff programmes on medical errors

The leading cause of serious medical errors is miscommunication between medical professionals. With little multicentre studies assessing programmes to improve handover between staff, a prospective intervention study assessed such a programme.

A handoff improvement programme consisted of a mnemonic to standardise handovers; handoff and communication training; faculty development; and an observation programme and sustainability campaign.

The study was carried out in nine hospitals and primary outcomes where medical errors and preventable adverse events.

Medical error rates decreased by 23% between the period of pre-intervention and post-intervention. Preventable adverse events also decreased by 30%. There was no change in non-preventable adverse events. Significant error reductions were found at 6 of the sites during site level analyses. There was no significant change in the time taken for oral handoffs or workflow.

This study found that the programme decreased medical errors and preventable adverse events without any negative effects on workflow.

Starmer A, Spector N, Srivastava R, et al. Changes in Medical Errors after Implementation of a Handoff Program. *NEJM* 2014; 371: 1803–1812.

Sickle cell trait and chronic kidney disease in African Americans

Chronic kidney disease (CKD) is associated with sickle cell disease, but the sickle cell trait (SCT) has only been linked to impaired urinary concentration, asymptomatic haematuria and papillary necrosis. No link between CKD and SCT has been established.

A recent analysis of large prospective studies evaluated the development of CKD in African Americans both with and without the SCT. A total of 15 975 participants were evaluated, 1248 patients had the SCT. The primary outcomes were the incidence of CKD, decline in Glomerular filtration rate (eGFR) and the presence of albuminuria.

The odds ratio (OR) and absolute risk difference (ARD) for CKD in patients with the SCT was 1.57 and 7.6% respectively. The OR of a decline in eGFR was 1.32 and ARD of 6.1% in patients with the SCT.

The findings show an increased risk of CKD, decline in eGFR and albuminuria in patients with SCT.

Naik R, Derebail V, Grams M, et al. Association of sickle cell trait with chronic kidney disease and albuminuria in African Americans. *JAMA* 2014; 312: 2115–2125.

CPD Challenge
See page 46 to test yourself on this article