research update

FROM THE JOURNALS Edited highlights of Richard Lehman's blog on http://bmj.co/Lehman

Spooky RSV trial

There's a hint of Porton Down about this phase 1 study of an oral treatment for respiratory syncytial virus (RSV). The 62 volunteers trooped in and the steel doors shut behind them. Two days later, masked personnel in white coats proceeded to inoculate them intranasally with four log_{10} plaque forming-units of the RSV-A Memphis 37b challenge virus. The volunteers spent another two days in quarantine and were then monitored twice daily for signs of incipient RSV infection. Once these signs appeared, nasal samples were sent off for a polymerase chain reaction test to confirm RSV, and the volunteers were then given the mystery drug ALS-008176, or a placebo. At this point Sherlock broke into the secret chamber, the lights went out, klaxons sounded, and the experiment had to be aborted. Ah no, that was just for the television: in real life, the volunteers continued to languish in durance vile for two weeks. Those given the active drug had fewer symptoms and a smaller weight of collected snot, so showing some potential benefit from ALS-008176 in healthy adults with previous immune memory of RSV. This is an orally bioavailable prodrug of the novel RSV replication inhibitor ALS-008112, a cytidine nucleoside analogue. One has to believe there was some good reason that this Alios BioPharma study appears in the *New England Journal of Medicine*, even though this drug needs two further rounds of testing in scenarios that bear some approximation to real life.

N Engl J Med 2015, doi:10.1056/NEJMoa1413275

US hospitals showing COURAGE

As I wrote last week in connection with long term follow-up from the COURAGE trial, interventional cardiologists can be slow to unlearn the oculostenotic reflex, whereby whenever they see a stenosis they insert a stent, with a minimum of cerebral processing. Nihar Desai's survey of coronary intervention in American hospitals stretches from two years after the publication of COURAGE to last year (2009-14), and is a classic in the literature of variation and de-adoption in medical practice. What Glover discovered about needless tonsillectomy in the 1930s is still incompletely enacted in practice today. What COURAGE demonstrated in 2007 about stable coronary disease is showing similarly patchy adoption: "there have been significant reductions in the volume of nonacute PCI [percutaneous coronary intervention]. The proportion of nonacute PCIs classified as inappropriate has declined, although hospital level variation in inappropriate PCI persists."

JAMA 2015, doi:10.1001/jama.2015.13764

Andexanet the Factor Xa antidote

And now it's the turn of some healthy older volunteers to test a drug produced by Portola Pharmaceuticals. No need for any fancy doors and masks here, though the 101 participants of this phase 2 trial still enjoyed the hospitality of the study centre for eight days. Over the first four days, they were given either apixaban or rivaroxaban, which (as you should know by now) are direct inhibitors of factor Xa. They then received a one hour infusion of either placebo or andexanet. Don't worry if this name is strange to you: it is a recombinant modified human factor Xa decoy protein that is catalytically inactive but retains the ability to bind factor Xa inhibitors in the active site with high affinity and a 1:1 stoichiometric ratio. In other words, it is a very expensive prospective antidote to these expensive new anticoagulants. For the volunteers, it worked perfectly: "Andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration and for the duration of infusion, without evidence of clinical toxic effects," purrs the conclusion of the abstract.

Help, I'm in a fix! - oh man,
He's bleeding on apixaban!
"Shush, here's some andexanet,
Bung it in and cease to fret."

In fact, as the accompanying editorial points out, we are well short of knowing how this drug will perform in the messy emergencies of real clinical practice.

N Engl J Med 2015, doi:10.1056/NEJMoa1510991

CLEAN those easy-to-reach germs

In a challenge to his powers of chemical analysis, Sir Humphry Davy was presented with some purple-brown crystals when he boldly visited Napoleon's Paris in 1813. He correctly identified them as a new element, which he called iodine, and claimed its discovery for Britain. It is hard to know whether he did this for his own vainglory or just to miff the French. He succeeded in annoying everybody and laying the ground for the use of alcoholic solutions of iodine as a medical antiseptic. By contrast, the medical antiseptic chlorhexidine is truly British. It was discovered in the early 1950s when the Imperial Chemical Industries was trying to produce new anti-malarial drugs. French physicians have now carried out the CLEAN trial comparing skin cleansing using povidone-iodine versus chlorhexidine alcohol solutions for preventing intravascular catheter related infections. They have proved that British chlorhexidine works better than French/British iodine.

Lancet 2015, doi:http://dx.doi.org/10.1016/S0140-6736(15)00244-5

Cite this as: *BMJ* 2015;351:h6306

Is there a weekend effect in obstetrics?

ORIGINAL RESEARCH Observational study

Association between day of delivery and obstetric outcomes

Palmer WL, Bottle A, Aylin P

Cite this as: *BMJ* 2015;351:h5774

Study question What is the association between day of delivery and measures of quality and safety of maternity services, particularly comparing weekend with weekday performance?

Methods This observational study examined outcomes for maternal and neonatal records (1 332 835 deliveries and 1 349 599 births between 1 April 2010 and 31 March 2012) within the nationwide administrative dataset for English National Health Service hospitals by day of the week. Groups were defined by day of admission (for maternal indicators) or delivery (for neonatal indicators) rather than by day of complication. Logistic regression was used to adjust for case mix factors including gestational age, birth weight, and maternal age. Staffing factors were also investigated using multilevel models to evaluate the association between outcomes and level of consultant presence. The primary outcomes were perinatal mortality and—for both neonate and mother—infections, emergency readmissions, and injuries.

Study answer and limitations Performance across four of the seven measures was significantly worse for women admitted, and babies born, at weekends. In particular, the perinatal mortality rate was 7.3 per 1000 babies delivered at weekends, 0.9 per 1000 higher than for weekdays (adjusted odds ratio 1.07, 95% confidence interval 1.02 to 1.13). No consistent association between outcomes and staffing was identified, although trusts that complied with recommended levels of consultant presence had a perineal tear rate of 3.0% compared with 3.3% for non-compliant services (adjusted odds ratio 1.21, 1.00 to 1.45). Limitations of the analysis include the method of categorising performance temporally, which was mitigated by using a midweek reference day (Tuesday). Further research is needed to investigate possible bias from unmeasured confounders and explore the nature of the causal relationship.

What this study adds This study provides an evaluation of the "weekend effect" in obstetric care, covering a range of outcomes. The results would suggest approximately 770 perinatal deaths and 470 maternal infections per year above what might be expected if performance was consistent across women admitted, and babies born, on different days of the week.

Funding, competing interests, data sharing The research was partially funded by Dr Foster Intelligence and the National Institute for Health Research (NIHR) Imperial Patient Safety Translational Research Centre in partnership with the Health Protection Research Unit (HPRU) in Healthcare Associated Infection and Antimicrobial Resistance at Imperial College London. WLP was supported by the National Audit Office.

COMMENTARY Evidence points to higher weekend risks for mothers and babies

The weekend effect is particularly understudied in obstetrics, so Palmer and colleagues' new thoughtful analysis is welcome.[8]

They found that some adverse outcomes were slightly but significantly more common among weekend deliveries, most notably perinatal mortality. Although the magnitude was small, the gravity of this outcome demands our attention. Despite some notable null findings,[4] enough evidence now exists for us to reasonably suspect that out of hours deliveries are at higher risk for adverse outcomes.[6-8] However, additional well designed studies are needed to determine whether these findings are robust within and across populations.

The weekend effect in obstetrics fits within the broad concept of "capacity strain" in healthcare systems—the process by which performance of a clinical unit can deteriorate above a certain threshold of patient volume, complexity (acuity), or both.[17 18] That threshold may well be lower at weekends, given the decreased levels of staffing and availability of resources that characterise most hospitals "out of hours." Evidence is emerging that other factors related to capacity strain such as busy days, holidays, and doctors' absence at conferences affect patients' outcomes, in addition to weekend effects.[7 19 20]

When a child is born . . . how much does it matter?

Factors that may help to mitigate the weekend effect and other forms of capacity strain in obstetric units include specific staffing models, such as the obstetric hospitalist model and other flexible models of care,[21] and hospital policies including condition specific protocols. Unfortunately, several recent studies have found no association between outcomes and staffing or use of protocols.[22 23]

Still, we must continue to explore the factors that differentiate obstetric units from one another, analyse how and when adverse outcomes "out of hours" are associated with these factors, and apply the findings to clinical practice and hospital policy. In the end, weekend delivery is an inevitable part of everyday practice. Solutions will require extra resources, systems thinking, and all our creativity, to determine what explains the apparent protective effect of weekday delivery and how to extend these benefits to women who deliver at the weekend, and their babies.

> Solutions will require extra resources, systems thinking, and all our creativity

Cite this as: *BMJ* 2015;351:h6192

Jonathan M Snowden, assistant professor, Department of Obstetrics and Gynecology and School of Public Health, Oregon Health and Science University, Portland, OR 97239, USA Snowden@ohsu.edu
Aaron B Caughey, professor and chair, Department of Obstetrics and Gynecology, Oregon Health and Science University

Methylphenidate for ADHD

ORIGINAL RESEARCH Cochrane systematic review with meta-analyses and trial sequential analyses of randomised clinical trials

A puzzle still in need of solutions

Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents

Storebø OJ, Krogh HB, Ramstad E, et al
Cite this as: *BMJ* 2015;351:h5203

Study question Is methylphenidate beneficial or harmful for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents?

Methods Electronic databases were searched up to February 2015 for parallel and crossover randomised clinical trials comparing methylphenidate with placebo or no intervention in children and adolescents with ADHD. Meta-analyses and trial sequential analyses (TSA) were conducted. Quality was assessed using GRADE. Teachers, parents, and observers rated ADHD symptoms and general behaviour.

Study answer and limitations The analyses included 38 parallel group trials (n=5111, median treatment duration 49 days) and 147 crossover trials (n=7134, 14 days). The average age across all studies was 9.7 years. The analysis suggested a beneficial effect of methylphenidate on teacher rated symptoms in 19 parallel group trials (standardised mean difference (SMD) −0.77, n=1698), corresponding to a mean difference of −9.6 points on the ADHD rating scale. There was no evidence that methylphenidate was associated with an increase in serious adverse events (risk ratio 0.98, nine trials, n=1532; TSA adjusted intervention effect RR 0.91). Methylphenidate was associated with an increased risk of non-serious adverse events (1.29, 21 trials, n=3132; TSA adjusted RR 1.29). Teacher rated general behaviour seemed to improve with methylphenidate (SMD −0.87, five trials, n=668) A change of 7 points on the child health questionnaire (CHQ) has been deemed a minimal clinically relevant difference. The change reported in a meta-analysis of three trials corresponds to a mean difference of 8.0 points on the CHQ (range 0-100 points), which suggests that methylphenidate may improve parent reported quality of life (SMD 0.61, three trials, n=514). 96.8% of trials were considered high risk of bias trials according to the Cochrane guidelines. All outcomes were assessed very low quality by GRADE.

What this study adds The results suggest that among children and adolescents with a diagnosis of ADHD, methylphenidate may improve teacher reported symptoms of ADHD and general behaviour and parent reported quality of life. However, given the risk of bias in the included studies, and the very low quality of outcomes, the magnitude of the effects is uncertain, and the strength of evidence insufficient to guide practice. Methylphenidate is associated with an increased risk of non-serious but not serious adverse events.

Funding, competing interests, data sharing Region Zealand Research Foundation and Copenhagen Trial Unit. Competing interests are given in the full paper on bmj.com. Full data are available in the version of this review published in The Cochrane Library.

COMMENTARY Long term outcome data from a variety of research designs are urgently needed

Many unknowns still overshadow the clinical needs of those living with ADHD. Challenges include a lack of gold standard diagnostic measures, a blurred boundary between what is "normal" and "the condition," and poor academic and clinical consensus as to the best treatment approaches and outcome measurements. Research studies are heterogenous and treatment effects hard to assess.

Storebø and colleagues present a comprehensive and rigorous systematic review and meta-analysis of the use of methylphenidate in young people with ADHD.[4] Its findings are potentially important but confusing for clinicians and affected families, thanks to the poor overall quality of the evidence. Notably, they found "high quality data" gathered from just 183 participants in six trials, out of a potential 12 245 participants in the 185 trials included. The median duration of treatment was just two months.

Research into ADHD is in a sorry state. Inadequate funding for mental health research, combined with practical, ethical, and cultural barriers to conducting research on children, limit the generalisability of findings from all existing studies.[5]

We need to work more collaboratively, using multiple research designs, including observational research and qualitative research reporting patients' and carers' own perspectives. Given the barriers to conducting large trials in children, we must make full use of other sources of data, while not ignoring clinical consensus.[7]

More research is needed on the harms associated with drugs for treating ADHD. Trials are rarely powerful enough to evaluate uncommon but serious adverse events. Again, observational designs using register data and prescription databases are important alternative approaches.[8]

Finally, the woeful lack of understanding of what happens long term to children with ADHD is unfortunate considering the numbers affected. Researchers should now consider the long term trajectory of clinical decision making, which includes functional assessments of relationships and educational outcomes, best done after six months. At this point, clinicians are working outside the scope of existing short term evidence.

Determining the clinically appropriate use of drugs is not a simple task in a condition such as ADHD, which lies at the intersection between cultural expectations of behaviour, parental concerns about using psychoactive substances, and children's changing development. Identifying and dealing with the priority domains of functioning for each child must be at the forefront of our work. This latest systematic review and meta-analysis is yet another reminder that we need a more meaningful research agenda to test the long term consequences of treatments for ADHD. For now, the jury is still out.

Cite this as: *BMJ* 2015;351:h5875

Mina Fazel, NIHR postdoctoral research fellow, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK
Mina.fazel@psych.ox.ac.uk

Folic acid fortification for Europe?

ORIGINAL RESEARCH Population based study

Long term trends in prevalence of neural tube defects in Europe

Khoshnood B, Loane M, de Walle H, et al

Cite this as: *BMJ* 2015;351:h5949

Study question What are the long term trends in the total (live births, fetal deaths, and terminations of pregnancy for fetal anomaly) and live birth prevalence of neural tube defects (NTD) in Europe, where many countries have issued recommendations for folic acid supplementation but a policy for mandatory folic acid fortification of food does not exist?

Methods This was a population based, observational study using data on 11 353 cases of NTD not associated with chromosomal anomalies, including 4162 cases of anencephaly and 5776 cases of spina bifida from 28 EUROCAT (European Surveillance of Congenital Anomalies) registries covering approximately 12.5 million births in 19 countries between 1991 and 2011. The main outcome measures were total and live birth prevalence of NTD, as well as anencephaly and spina bifida, with time trends analysed using random effects Poisson regression models to account for heterogeneities across registries and splines to model non-linear time trends.

Summary answer and limitations Overall, the pooled total prevalence of NTD during the study period was 9.1 per 10 000 births. Prevalence of NTD fluctuated slightly but without an obvious downward trend, with the final estimate of the pooled total prevalence of NTD in 2011 similar to that in 1991. Estimates from Poisson models that took registry heterogeneities into account showed an annual increase of 4% (prevalence ratio 1.04, 95% confidence interval 1.01 to 1.07) in 1995-99 and a decrease of 3% per year in 1999-2003 (0.97, 0.95 to 0.99), with stable rates thereafter. The trend patterns for anencephaly and spina bifida were similar, but neither anomaly decreased substantially over time. The live birth prevalence of NTD generally decreased, especially for anencephaly. Registration problems or other data artefacts cannot be excluded as a partial explanation of the observed trends (or lack thereof) in the prevalence of NTD.

What this study adds In the absence of mandatory fortification, the prevalence of NTD has not decreased in Europe despite longstanding recommendations aimed at promoting peri-conceptional folic acid supplementation and existence of voluntary folic acid fortification.

Funding, competing interests, data sharing The study was funded by the European Public Health Commission, EUROCAT Joint Action 2011-2013. HdeW and ML received support from the European Commission DG Sanco during the conduct of this study. No additional data available.

COMMENTARY Europe should consider mandatory fortification

In 1991 the UK Medical Research Council published the exciting finding that women who took folic acid before conception could reduce their babies' risk of a neural tube defect by as much as 72%.[1] The US Public Health Service met and quickly issued a recommendation that all women of childbearing age capable of becoming pregnant should take 400 µg folic acid daily.[2] Some of us who attended the meeting had doubts that women would take folic acid as instructed. In fact, many folate related neural tube defects were not prevented despite this recommendation and voluntary fortification in the United States. This led the United States to institute mandatory fortification in 1998.[3] Almost 80 countries now have similar programmes, and have experienced dramatic falls in rates of neural tube defects. Given the US experience, it is not surprising that Khoshnood and colleagues have shown that the European Union's current strategy, although useful, is failing to prevent many folate related neural tube defects.[4]

> Fortification would prevent approximately half of all neural tube defects

Fortification would prevent approximately half of all neural tube defects.[5] From both human and financial perspectives, this is a great benefit. One major problem is the masking of the diagnosis of vitamin B_{12} deficiency when high doses (>1 mg/day) are consumed.

Other benefits and risks are less clear. In particular, the EU could use some standard criteria to determine whether folic acid is causally associated with cancer: the data do not show consistent positive associations between folic acid and various cancers; the strength of association is weak, if present at all; and biological plausibility could be argued either way. What does folic acid do to pre-malignant lesions? Again, the limited data are inconsistent. There is no coherence across various types of study, so another criterion is not met. The evidence to date does not demonstrate a causal link between fortification and cancer. Because cancer is very common, however, even a small increase in relative risk, if real, could cause a serious increase in the number of cancers.

Time for yes vote on compulsory fortification?

One of the challenges to implementing compulsory fortification is choosing a level that will prevent neural tube defects without exposing the population to excessive doses. Current levels of fortification in the United States provide on average 163 µg/day to women of childbearing age.[10] This level is highly successful in preventing folate related neural tube defects.[11 12]

Mandatory fortification has been shown to work in many countries. No important adverse effects have been identified to date, probably because a modest level of fortification has proved very effective. Authorities in the EU should take a further look at mandatory fortification.

Cite this as: *BMJ* 2015;351:h6198

James L Mills, senior biomedical research service scientist millsj@mail.nih.gov
Aggeliki Dimopoulos, IRTA postdoctoral fellow, Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892, USA