research update

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

Treating malaria in pregnancy

Here's a tonic for those of us who lie abed with thoughts about the stupidity of the world and the pointlessness of medical research. The PREGACT trial was supported by the European & Developing Countries Clinical Trials Partnership and it tells doctors in Africa exactly what they need to know: which is the best treatment out of four commonly used combinations to treat malaria in pregnancy? The bottom line is that currently the best choice in Africa seems to be dihydroartemisinin-piperaquine. The manufacturers of the various drugs donated them to the project, and without commercial support the triallists used simple robust randomisation methods and good ascertainment. It can be done like this. It should be done like this.

N Engl J Med 2016, doi:10.1056/NEJMoa1508606

Preventing malaria in pregnancy

And here is another great example of doing it like this. This time the sponsor was the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the question was to determine which prophylactic antimalarial might best replace sulfadoxine-pyrimethamine during pregnancy. The trouble with prophylaxis is of course that you create selection pressure in favour of the most resistant parasites, even if you only use it intermittently. So in countries such as Uganda, sulfadoxine-pyrimethamine is inevitably losing some of its effectiveness. The alternatives tested here were a three dose regimen of dihydroartemisinin-piperaquine and a monthly regimen of dihydroartemisinin-piperaquine. The latter proved best at preventing malaria in pregnant Ugandan women.

N Engl J Med 2016, doi:10.1056/NEJMoa1509150

Peanuts and the babes of London

Peanuts are unnecessary. They have been a food of last resort for humans for about 7000 years in South America, and for about 80 years in North America. Any food that contains peanuts would be better off without them. I hope I have made my position on the peanut question clear. However, it is not universally shared, and total peanut avoidance has become difficult in the 21st century. Hence the need to protect future generations from peanut related diseases, mostly in the form of allergy. You can do this by feeding peanuts to your infants in the first year of life, as in the LEAP trial. That way they are 80% less likely to show allergy to peanuts at age 5 years. The LEAP-on trial went on for an additional 12 months and sheds further light on this question, and 32 000 or more people have made this the second most sought after article on the *NEJM* website. The primary outcome in the follow-up trial was the percentage of participants with peanut allergy after 12 months of peanut avoidance. It made no difference. Personally, I would recommend a minimum avoidance period of 100 years.

N Engl J Med 2016, doi:10.1056/NEJMoa1514209

Glucose control in older people with diabetes

The greatest pleasure I get out of medicine these days is seeing brilliant youngsters doing stuff that I have long yearned to see done. After I wrote a *BMJ* editorial on glycaemic control in stable type 2 diabetes with Harlan Krumholz in 2009, I made a trip to Yale University with John Yudkin and met a young endocrinologist and scholar called Kasia Lipska. And now, eight years after the key trials appeared, Kasia has published several articles which should finally overturn the current model of overtreatment for type 2 diabetes in elderly people. "High-quality evidence about glycemic treatment in older adults is lacking. Optimal decisions need to be made collaboratively with patients, incorporating the likelihood of benefits and harms and patient preferences about treatment and treatment burden. For the majority of older adults, an HbA1c target between 7.5% and 9% will maximize benefits and minimize harms."

JAMA 2016, doi:10.1001/jama.2016.0299

NSTEMI in very old people

If my present levels of fatalism persist, I shan't very much care if I live or die after the age of 80. On the other hand, I wouldn't like to inconvenience my loved ones by having a disabling stroke or repeated heart attacks. So this Norwegian trial gives me some useful information to use if I happen to get a non-ST elevation myocardial infarction at or beyond the age of 80. It makes no difference to my likelihood of death over a year and a half whether I have immediate invasive treatment or just medical treatment. But if I go for the latter, there's a much greater chance of having to go back for an emergency procedure, and it gives me a 48% greater risk of another myocardial infarction and possibly a higher risk of stroke. So I'd probably opt for percutaneous coronary intervention.

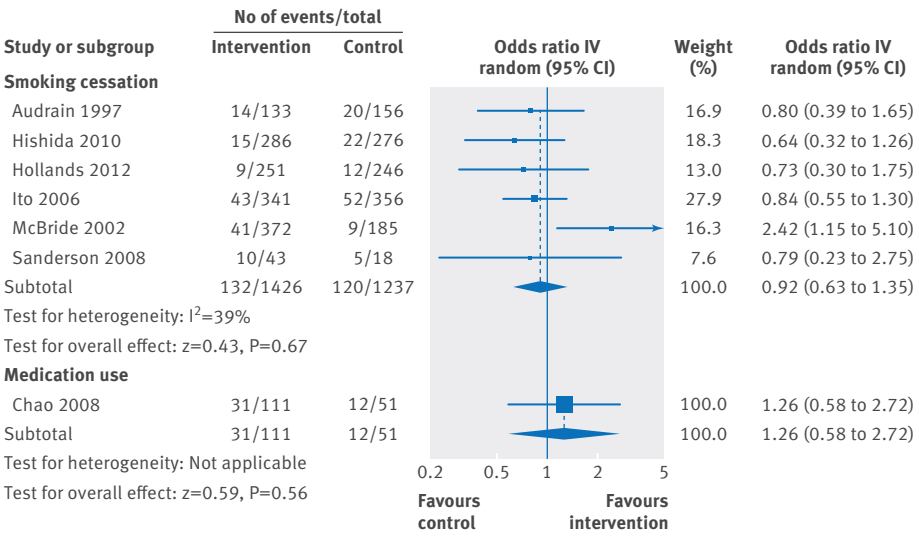
Lancet 2016, doi:http://dx.doi.org/10.1016/S0140-6736(15)01166-6

ORIGINAL RESEARCH Systematic review and meta-analysis

The impact of communicating genetic risks of disease on risk-reducing health behaviour

Hollands GJ, French DP, Griffin SJ, et al

Cite this as: *BMJ* 2016;352:i1102
Find this at: http://dx.doi.org/10.1136/bmj.i1102



Primary outcome analysis: smoking cessation; medication use

Study question Does communicating genetic risks motivate risk-reducing behaviour change?

Methods For this systematic review and meta-analysis, the authors identified eligible studies by systematically searching five electronic databases and by citation searching. Eligible studies were randomised controlled trials involving adults in which one group received personalised DNA based disease risk estimates for diseases for which the risk could be reduced by behaviour change. The primary outcomes were measures of risk-reducing health behaviour, such as stopping smoking, improving diet, or increasing levels of physical activity.

Study answer and limitations There were no statistically significant effects of communicating DNA based risk estimates on any risk-reducing behaviours. However, the studies that were included were often of low quality.

What this study adds This review provides the most conclusive evidence to date that communicating DNA based disease risk estimates has little or no effect on risk-reducing health behaviour.

Funding, competing interests, data sharing This review was funded by Medical Research Council and National Institute for Health Research awards. The authors have no competing interests to declare.

RESEARCH METHODS AND REPORTING Evidence reporting and assessment checklist

Guidelines for reporting of health interventions using mobile phones

Agarwal S, LeFevre AE, Lee J, et al; for the WHO mHealth Technical Evidence Review Group

Cite this as: *BMJ* 2016;352:i1174
Find this at: http://dx.doi.org/10.1136/bmj.i1174

The past decade has seen a rapid increase in health interventions using mobile devices to improve the delivery of services, engagement of clients, and strengthening of health system functions (mHealth). Despite much investment in this field, the evidence base to support specific digital strategies remains weak. Part of this challenge stems from variable quality and comprehensiveness in the reporting of these projects and programmes. The use of reporting guidelines can help in standardising the reporting of evidence, and allow decision makers to synthesise and better understand the state of evidence.

To support such improvements, the World Health Organization convened the mHealth Technical Evidence Review Group—a group of global experts working at the intersection of mHealth research and implementation. The group recommended the development of the mHealth evidence reporting and assessment (mERA) checklist. These 16 checklist criteria were developed to identify a minimum set of information needed to define what the mHealth intervention is (content), where it is being implemented (context), and how it is implemented (technical features), to support replication of the intervention. Like similar checklists, mERA does not attempt to evaluate the quality of the research, but rather the quality of the reporting of the research and the mHealth intervention.

Consistent use of this checklist should aid authors in reporting mHealth project findings more comprehensively, guide reviewers and policy makers in synthesising high quality evidence, and guide journal editors in critically assessing the transparency and completeness in the reporting of mHealth studies.

Core items of the mERA checklist

1 Infrastructure (population level)
2 Technology platform
3 Interoperability/health information systems context
4 Intervention delivery
5 Intervention content
6 Usability/content testing
7 User feedback
8 Access of individual participants
9 Cost assessment
10 Adoption Inputs/programme entry
11 Limitations for delivery at scale
12 Contextual adaptability
13 Replicability
14 Data security
15 Compliance with national guidelines or regulatory statutes
16 Fidelity of the intervention

Antibiotic resistance in children with *E coli* UTI

ORIGINAL RESEARCH Systematic review and meta-analysis

Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli* and association with routine use of antibiotics in primary care

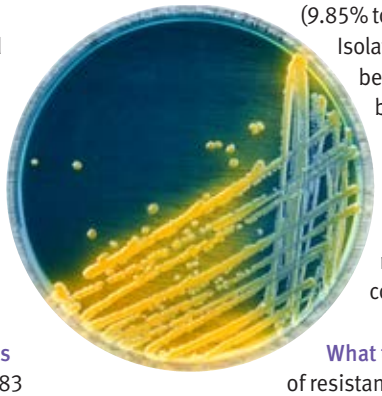
Bryce A, Hay AD, Lane IF, Thornton HV, Wootton M, Costelloe C

Cite this as: *BMJ* 2016;352:i939

Find this at: http://dx.doi.org/10.1136/bmj.i939

Study question What is the prevalence of antibiotic resistance caused by *Escherichia coli* in urinary tract infections in children and is there a relation between previous antibiotics prescribed in primary care and resistance?

Methods Studies were eligible for systematic review if they reported resistance in community acquired urinary tract infection caused by *E coli* in children and young people aged 0-17. The pooled prevalence of resistance to commonly used primary care antibiotics in children, stratified by the OECD (Organisation for Economic Co-operation and Development) status of the study country, was calculated. Random effects meta-analysis was used to quantify the association between previous exposure to antibiotic and resistance.



Study answer and limitations 58 studies investigated 77 783 *E coli* urinary isolates. In studies in OECD countries, the pooled prevalence of resistance was 53.4% (95% confidence interval 46.0% to 60.8%) to ampicillin, 23.6% (13.9% to 32.3%) to trimethoprim, 8.2% (7.9% to 9.6%) to co-amoxiclav, and 2.1% (0.8% to 4.4%) to ciprofloxacin; resistance to nitrofurantoin was the lowest at 1.3% (0.8% to 1.7%). In non-OECD countries resistance was significantly higher: 79.8% (73.0% to 87.7%) to ampicillin, 60.3% (40.95 to 79.0%) to co-amoxiclav, 26.8% (11.15 to 43.0%) to ciprofloxacin, and 17.0% (9.85% to 24.2%) to nitrofurantoin. Isolates were more likely to be resistant if children had been previously prescribed antibiotics, and this increased risk can persist for up to six months. The main limitation was accurate measurement of over the counter antibiotic use.

What this study adds Prevalence of resistance to commonly prescribed antibiotics in primary care for urinary tract infections in children caused by *E coli* is high, particularly in non-OECD countries, where one possible explanation is the availability of over the counter antibiotic. This could render some antibiotics ineffective as first line treatments for urinary tract infection.

Funding, competing interests, data sharing AB is supported by a doctoral fellowship from the NIHR School for Primary Care Research. ADH is supported by a NIHR research professorship. All authors declared no competing interests. No data are available for sharing.

COMMENTARY An emerging global problem that will change clinical management

Bryce and colleagues present compelling evidence of the need to reconsider current approaches to community based management of paediatric urinary tract infection. Their findings confront long established patterns of practice and are inextricably linked to the emerging global problem of antimicrobial resistance.

For an antibiotic to be considered a first line empirical treatment, resistance should not exceed 20% in the most likely infecting strain. This threshold has clearly been reached for many antibiotics used for paediatric *E coli* urinary tract infection. Bryce and colleagues also find that previous antibiotic use in primary care increased the subsequent risk of *E coli* resistance.

All change

Guidelines for "first choice" antibiotics in this setting should be revisited. Clinicians will need access to up to date data on patterns of resistance within and beyond their own jurisdictions, and primary care clinicians will probably need to get used to taking an "antibiotic history" before prescribing for common bacterial infections. A parent's claim that "antibiotic x always works for my child" might need to be balanced with the notion that "if antibiotic x was used in the last six months, there's a good chance that it's not going to work as well if used again." Bryce and colleagues' findings mirror dramatic increases in resistance to drugs commonly used to manage *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* infections.

> Clinicians will probably need to get used to taking an "antibiotic history" before prescribing for common bacterial infections

Everyone can be seen as acting "rationally" with antibiotics: legislators promote availability when they allow antibiotics to be dispensed without prescription; doctors act to satisfy patients seeking relief from troubling symptoms; and farmers augment feed with antibiotics to increase food supply. The livestock producer, the legislator, the harried physician, and the anxious patient never feel the consequences of their decisions directly, yet their combined actions reduce the availability of effective antibiotics for everyone.

The World Health Organization's 2014 global action plan on antimicrobial resistance asks nations to adopt "whole of society" approaches to prevention, to enhance and better disseminate knowledge on antimicrobial resistance, and to develop an economic case for new investments in drugs, diagnostic tools, and vaccines.

This new systematic review joins a host of recent studies, reports, and calls to action on this issue. While I have no doubt that clinical practice guidelines will quickly be able to accommodate the findings, I am less confident that there is the will and commitment to deal with what WHO has called "the post-antibiotic era."

Grant Russell grant.russell@monash.edu

See thebmj.com for author details

Cite this as: *BMJ* 2016;352:i1399

Find this at: http://dx.doi.org/10.1136/bmj.i1399

Non-affective psychosis in refugees

ORIGINAL RESEARCH Cohort study of 1.3 million people in Sweden

Refugee migration and risk of schizophrenia and other non-affective psychoses

Hollander A-C, Dal H, Lewis G, Magnusson C, Kirkbride JB, Dalman C

Cite this as: *BMJ* 2016;352:i1030
Find this at: http://dx.doi.org/10.1136/bmj.i1030

Study question Are refugees at elevated risk of non-affective psychotic disorders, including schizophrenia, relative to other migrants and the Swedish-born population?

Methods This was a cohort study of people living in Sweden, born after 1 January 1984 and followed until diagnosis of non-affective psychotic disorder, emigration, death, or 31 December 2011, using linked Swedish national register data. The study included 1 347 790 people, including native Swedes (1 191 004; 88.4%), refugees (24 123; 1.8%), and non-refugee migrants (132 663; 9.8%) from the Middle East and north Africa, sub-Saharan Africa, Asia, and eastern Europe and Russia. Cox regression estimated adjusted hazard ratios, controlling for age at risk, sex, disposable income, and population density.

Study answer and limitations Crude incidence rates were 38.5 (95% confidence interval 37.2 to 39.9) per 100 000 person years in Swedish-born people, 80.4 (72.7 to 88.9) in non-refugee migrants, and 126.4 (103.1 to 154.8) in refugees. Refugees were at increased risk of psychosis compared with both the Swedish-born population (adjusted hazard ratio 2.9, 2.3 to 3.6) and non-refugee migrants (1.7, 1.3 to 2.1). Rates were increased in refugees compared with non-refugees from all regions of origin, except sub-Saharan Africa. As the study was based on Swedish registers, information on pre-migratory experiences was unavailable.

What this study adds Refugees face increased risk of schizophrenia and other non-affective psychotic disorders, compared with non-refugee migrants from similar regions and the native-born Swedish population. Clinicians and health service planners in refugee receiving countries should be aware of a raised risk of psychosis in refugees.

Funding, competing interests, data sharing A-CH is supported by FORTE. JBK is supported by a Sir Henry Dale fellowship funded by the Wellcome Trust and Royal Society. CD is supported by the Swedish Research Council. JBK and CD are co-senior authors. Under Swedish law and ethical approval, patient level data cannot be made available.

JOHAN NILSSON/PA

Refugees arriving at Hyllie train station, Sweden

COMMENTARY Risk is exacerbated by adverse experiences after arrival

In 2015, 244 million people (3.3% of the world's population) lived outside their country of origin. Substantial evidence shows that the risk of non-affective psychosis is increased by a factor of about 2.5 in migrants compared with the indigenous population.

In the linked paper, Hollander and colleagues argue that this increase is due predominantly to exposure to psychosocial adversities. Their cohort study of more than 1.3 million people compared risk of non-affective psychosis between people born in Sweden and migrants to Sweden and also between refugees and non-refugees within the migrant group.

Incidence rates for non-affective psychosis were 385 per million in those born in Sweden, 804 per million in non-refugee migrants, and 1264 per million in refugees. It is perhaps of particular importance that the elevated rate in refugees was significant for all geographical areas of origin except sub-Saharan Africa. The authors suggest that this reflects the high rates of social adversity experienced by migrants from sub-Saharan Africa as a whole, as opposed to the more specific increase in adversity experienced by refugees from other parts of the world.

> These factors may include institutional detention, inability to work, destitution, and difficulty in accessing health and social care

Prolonged distress

The most obvious implication to be drawn from these findings is that refugees are particularly vulnerable to developing non-affective psychoses and that, as the authors state, we "need to take the early signs and symptoms of psychosis into account in refugee populations as part of any clinical mental health service response to current global humanitarian crises."

As Hollander and colleagues also point out, one of the key limitations of their study is the lack of information on post-migration risk factors such as racism and discrimination. Consideration also needs to be given to the challenges that asylum seekers face during what is often a prolonged and distressing process. These factors may include institutional detention, inability to work, destitution, and difficulty in accessing health and social care.

Both detention of immigrants and prolonged uncertainty about immigration are known to increase vulnerability to mental illness as a whole—this may well include increased vulnerability to non-affective psychosis. Another aspect characteristic of the current European refugee crisis has been the long and perilous journey many refugees face before reaching the country in which they seek protection.

The potential effect of a fair and responsive asylum system on mental health outcomes including non-affective psychosis remains to be determined. Meanwhile, however, a robust mental health response to the refugee "crisis" must lie in a combination of clinical vigilance, recognition of vulnerability factors, and, above all, a determination to minimise the aggravating effects of post-migration experiences.

Cornelius Katona cornelius@helenbamber.org
See thebmj.com for author details

Cite this as: *BMJ* 2016;352:i1279
Find this at: http://dx.doi.org/10.1136/bmj.i279