research update

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

Gingering up treatments for hyperemesis

I have a small advisory job with Cochrane UK, and a few months back we looked at a new review of treatments for hyperemesis gravidarum. I remember we all chuckled about the inclusion of ginger. Here is the conclusion of the Cochrane review: "On the basis of this review, there is little high-quality and consistent evidence supporting any one intervention, which should be taken into account when making management decisions . . . The limitations in interpreting the results of the included studies highlights the importance of consistency in the definition of hyperemesis gravidarum, the use of validated outcome measures, and the need for larger placebo-controlled trials." Here in *JAMA* comes a similar systematic review from a different (British) team reaching similar conclusions, although more positively expressed: "For mild symptoms of nausea and emesis of pregnancy, ginger, pyridoxine, antihistamines, and metoclopramide were associated with greater benefit than placebo. For moderate symptoms, pyridoxine-doxylamine, promethazine, and metoclopramide were associated with greater benefit than placebo. Ondansetron was associated with improvement for a range of symptom severity. Corticosteroids may be associated with benefit in severe cases. Overall the quality of evidence was low." Both conclusions are correct but highlight the problem of whether to make any mention of agents when the evidence for all of them is poor.

JAMA 2016, doi:10.1001/jama.2016.14337

MI: better care counts in long term

In a big survey of hospital quality rating and myocardial infarction outcomes Harlan Krumholz and his team show that prompt optimal management not only improves immediate survival but has life extending benefits for 17 or more years after. The management of myocardial infarction has also undergone five revolutions since the 1970s: the de-adoption of lidocaine (lignocaine), the adoption of aspirin, the introduction of thrombolysis, the diagnostic use of troponins, and the arrival of immediate percutaneous coronary intervention. Plus the early use of β blockers and the long term use of statins. These things work: medicine does achieve progress: evidence counts: putting it into practice even more so.

N Engl J Med 2016, doi:10.1056/NEJMoa1513223

Cold comfort for in-hospital arrest

Whole body freezing is for preserving dead people until science learns how to revive them, whereas whole body cooling is for preserving half dead people. Decades ago, ideas like this would have been called "boyish." Suffice to say that this observational study looks at the effect of induced hypothermia on patients with in-hospital cardiac arrest. Apparently it's become quite popular in some places, although there have been no randomised trials within hospitals. "Use of therapeutic hypothermia compared with usual care was associated with a lower likelihood of survival to hospital discharge and a lower likelihood of favorable neurological survival. These observational findings warrant a randomised clinical trial to assess efficacy of therapeutic hypothermia for in-hospital cardiac arrest." Or just dropping the whole idea?

JAMA 2016, doi:10.1001/jama.2016.14380

Dupilumab for eczema

With the new monoclonal antibody for eczema, things look a bit more straightforward. Dupilumab inhibits the actions of interleukin 4 and interleukin 13, which are important mediators of inflammation in atopic diseases. The SOLO 1 and SOLO 2 trials tested weekly or fortnightly dupilumab in adults with moderate to severe atopic dermatitis whose disease was inadequately controlled by topical treatment or for whom topical treatment was medically inadvisable. In both trials, 30% more of patients responded to the active drug given every two weeks than to placebo injections. Judging from the Kaplan-Meier charts, you could tell who would respond by about eight weeks, but this needs checking from individual participant data.

N Engl J Med 2016, doi:10.1056/NEJMoa1610020

Alternatives to admission

The UK has one of the lowest numbers of hospital beds per unit of population in the developed world, and levels of bed occupancy that would be considered dangerous by most criteria. Yet politicians and their favoured advisers still talk blithely of moving more acute medical care into the community. Here's a big systematic review of alternatives to hospital admission for acute medical conditions, which concludes that "for low-risk patients with a range of acute medical conditions, evidence suggests that alternative management strategies to inpatient care can achieve comparable clinical outcomes and patient satisfaction at lower costs." But here, context is everything. It depends on the robustness and capacity of the primary care workforce: I don't believe that you can generalise across health systems.

JAMA Intern Med 2016, doi:10.1001/jamainternmed.2016.5974

Non-specific effects of childhood vaccines

ORIGINAL RESEARCH Systematic review

Association of BCG, DTP, and measles containing vaccines with childhood mortality

Higgins JPT, Soares-Weiser K, López-López JA, et al

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Find this at: http://dx.doi.org/10.1136/bmj.i5170

Study question What is the evidence on the effects of Bacillus Calmette-Guérin (BCG), diphtheria-tetanus-pertussis (DTP), and standard titre measles containing vaccines (MCV) on mortality in children under 5?

Methods This was a literature based systematic review of epidemiological studies, selecting a single result from each non-overlapping group of children and including a detailed assessment of the risk of bias for each finding. It included clinical trials, cohort studies, and case-control studies comparing children who were and were not given one of the three vaccines and reporting mortality data for children up to 5 years of age.

Study answer and limitations Receipt of BCG (relative risk 0.70, 95% confidence interval 0.49 to 1.01, from clinical trials; 0.47, 0.32 to 0.69, from observational studies) or standard titre MCV (0.74, 0.51 to 1.07; 0.51, 0.42 to 0.63) was associated with a lower risk of all cause mortality. Receipt of DTP was associated with a higher risk of mortality in seven observational studies and a lower risk in two observational studies (overall relative risk 1.38, 0.92 to 2.08). All of the observational studies in these analyses were assessed to be at high risk of bias.

What this study adds This review suggests that receipt of BCG and standard titre MCV is associated with a lower risk of all cause mortality and that receipt of DTP may be associated with a higher risk of all cause mortality. The evidence available to date does not support a change to existing vaccination recommendations but indicates a need for randomised trials to examine the positioning of DTP in the vaccine schedule.

Funding, competing interests, data sharing The review, based on published literature, was funded by the World Health Organization.

ORIGINAL RESEARCH Systematic review

Non-specific immunological effects of selected routine childhood immunisations

Kandasamy R, Voysey M, McQuaid F, et al

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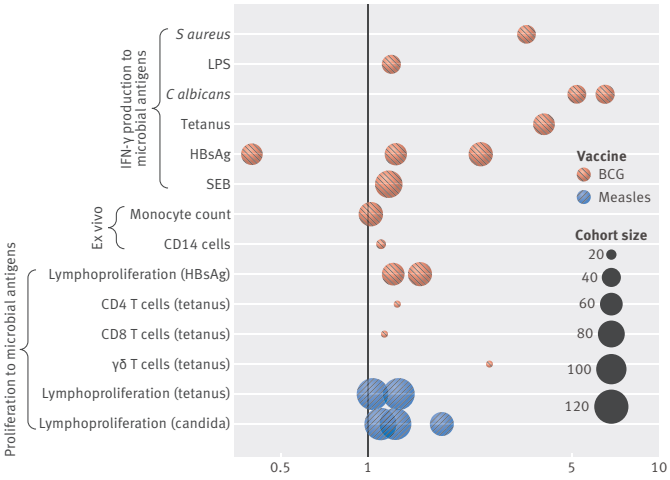
Find this at: http://dx.doi.org/10.1136/bmj.i5225

Study question Do routine childhood vaccinations (BCG, measles, pertussis, and tetanus) have immunological effects other than those against the target disease?

Methods Embase, Trip, Cochrane (1947 to December 2012), and PubMed (1947 to January 2014) were searched for published randomised controlled trials, cohort studies, and case-control studies; unpublished articles were sought from a group of experts. The target population was infants aged under 5 years, though inclusion of studies was not limited to this age group to ensure all relevant studies were identified. Outcomes measured were all reported non-specific immunological effects (NSIE), with age at vaccination, sex, and co-administration of vitamin A as possible effect measure modifiers.

Study answer and limitations 77 manuscripts from 11 168 references met the inclusion criteria for data analysis. In most studies (48%) BCG was the vaccine intervention. Most (68%) studies were exclusively in children. At least one non-specific immunological variable was reported as having a significant difference in 38% of the studies. While some studies showed evidence suggestive of NSIE, no consistent findings were identified that provide confidence in the nature, magnitude, or timing of NSIE in humans after these vaccines nor the clinical importance of the findings. Meta-analysis was not possible because of heterogeneity, and none of the trends, when evident, are statistically sound. Included studies were at high risk of bias. Over 140 different immunological variables were reported, which, in conjunction with the differences in measurement units and summary statistics, created a high number of combinations. Most studies were not specifically designed to measure NSIE with many of the P values for a specific variable reported only once and thus potentially due to chance.



Observed increases in effect of biologically relevant non-specific immunological responses in vaccinated people. Enhanced IFN-γ and cellular responses to microbial antigens (tetanus toxoid, *C albicans*, hepatitis B surface antigen, and *S aureus*) and activation of innate immune system (monocytes and/or CD14 cells). SEB=staphylococcal enterotoxin B; LPS=lipopolysaccharide

What this study adds While some evidence of changes in immunological variables has been observed, in this review there is no conclusive immunological evidence from previously conducted studies to support the presence of consistent, clinically relevant, geographically generalisable, NSIE after vaccination with BCG, diphtheria, pertussis, tetanus or measles containing vaccines. Further studies with well designed immunological endpoints, linked to epidemiological observations, are needed before considering any change to current vaccination policy based on NSIE.

Funding, competing interests, data sharing This work was supported by WHO. One author (AJP) has previously conducted clinical trials on behalf of Oxford University that were sponsored by manufacturers of vaccines but does not receive any personal payments from them. AJP's department has received unrestricted educational grants for courses and conferences from vaccine manufacturers. No additional data available.

COMMENTARY Evidence of any "off target" effects remains weak and vulnerable to biases

Non-specific effects of vaccines or "off target effects" as they are sometimes called can be defined as effects of a vaccine beyond their intended target pathogen or disease. These effects can be beneficial as well as harmful.[1-3] The published evidence on non-specific effects of childhood vaccines remain confusing, so the linked systematic reviews by Higgins and colleagues[4] and Kandasamy and colleagues[5] looking at clinical and immunological non-specific effects are welcome.

The systematic reviews were commissioned by the WHO Strategic Advisory Group of Experts (SAGE) to decide if there was enough evidence to consider changes in scheduling or co-administration of certain vaccines.[6] It is important to emphasise that the systematic reviews were not intended or designed to assess if these vaccines are safe or should continue to be recommended for children. It is beyond debate that BCG, diphtheria, tetanus, pertussis (DPT), and measles containing vaccines (MCV) are safe. These vaccines have saved the lives of millions of children. The reviews' findings must not be hijacked to argue against their recommended use.

Higgins and colleagues provide a comprehensive collation of available data from clinical trials and cohort and case-control studies on the impact of BCG, DPT, and MCV on non-specific and all cause mortality in children aged under 5.[4] Importantly, the authors used a robust assessment of risk of bias to evaluate all eligible studies and exclude those at "very high" risk of bias. Observational studies of vaccine effects are vulnerable to confounding—unwell children are less likely to be vaccinated—as well as misclassification bias of vaccination status.

These biases are directly relevant to the controversial finding that receipt of DPT could be associated with an increase in all cause mortality (relative risk 1.38, 95% confidence interval 0.92 to 2.08).[4] This figure must be interpreted with extreme caution as all 10 studies in the analysis were observational and classified as "high risk of bias." Most were from the same setting, limiting generalisability. Importantly, the authors found no randomised trial data on this association.

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These vaccines have saved the lives of millions of children. The reviews' findings must not be hijacked to argue against their recommended use

In contrast, what they did find were randomised trial data suggesting that BCG vaccine could reduce all cause mortality (relative risk 0.70, 95% confidence interval 0.49 to 1.01).[4] Clinical trials of MCV also suggested a possible protective effect against mortality, especially for girls, but the low numbers of deaths and short follow-up prevent confident conclusions.

Complementing the epidemiological review, Kandasamy and colleagues reviewed evidence for non-specific immunological effects of BCG (48% of included papers), measles, MMR, DTP, DT, and pertussis vaccines.[5] The Achilles' heel of all such studies is that we do not have any established immunological markers for clinically relevant non-specific effects. This is reflected in the large number (143) of different immunological outcomes in the reviewed papers.[5] Meta-analysis of these heterogeneous studies wasn't possible, but a systematic review did find a trend of increased IFN-γ levels in BCG vaccinated individuals relative to unvaccinated controls.[5] Reviewed studies also reported lymphoproliferation in response to exposure to tetanus toxoid and *Candida albicans* antigen in people who had received measles vaccine.[5] Finally, DTP, DT, and pertussis vaccines were found to be capable of generating immune responses—lymphocyte proliferation and production of various cytokines—to heterologous antigens.[5] The actual relevance of these findings in relation to non-specific immunological effects of vaccines remains unclear.

Taken together, the two systematic reviews suggest that vaccines could have non-specific effects, but the evidence remains weak. After reviewing both studies, the WHO's expert group (SAGE) rightly concluded that there was no need to modify current vaccination schedules or policies.[6]

Perhaps the most important message from these two well conducted systematic reviews is that further small observational studies will not take us any closer to the truth about non-specific effects of childhood vaccines. Inherent biases and confounders (especially unknown confounders) cannot be eliminated by simply doing more of the same. If randomised controlled trials are not feasible, large observational study designs incorporating innovative methods to control for confounders, conducted with standardised protocols across multiple settings and countries is the only alternative. Similarly, coordination, standardisation, and a systems approach in immunological research on non-specific effects is urgently required.

The rapid advancement in immunological methods and technologies could complicate the evidence base still further if they result in the proliferation of studies reporting new immunological variables of unknown clinical relevance. Ideally, both epidemiological and immunological efforts need to be integrated. If we fail to come together, it is highly likely that we will still be in the same situation when these systematic reviews are updated in five or even 10 years.

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Antenatal corticosteroids for maturity of term or near term fetuses

Saccone G, Berghella V

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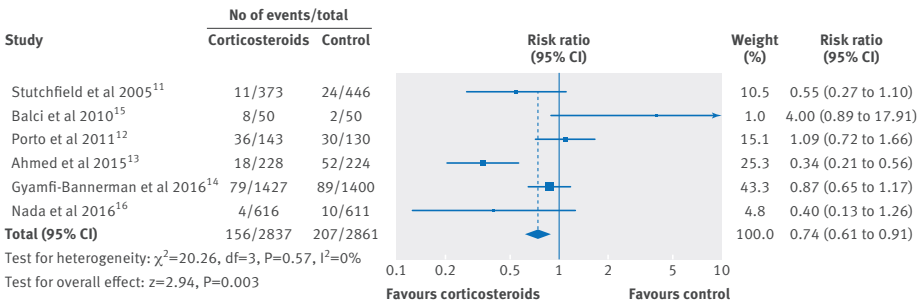
Study question How effective are antenatal corticosteroids given at or after 34 weeks' gestation at reducing neonatal respiratory morbidity?

Methods The authors searched several electronic databases to identify randomised controlled trials comparing use of antenatal corticosteroids with either placebo or no treatment in women with singleton pregnancies at or after 34 weeks' gestation. Included trials were on antenatal steroids given to women expected to deliver in late preterm pregnancy (34^0-36^6 weeks) and women before planned caesarean delivery at term (≥37 weeks). The primary outcome was the incidence of severe respiratory distress syndrome. Subgroup analyses for 34^0-36^6 weeks and 37 or more weeks were planned.

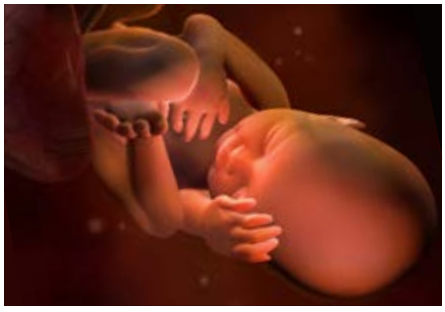
Study answer and limitations Six trials including 5698 singleton pregnancies were analysed. Three studies included 3200 women at 34^0-36^6 weeks' gestation and at risk of imminent premature delivery (either spontaneously or indicated) at the time of admission to hospital. The three other trials included 2498 women undergoing planned caesarean delivery at 37 or more weeks. Meta-analysis showed neonatal benefit of antenatal corticosteroids in women at immediate risk of late preterm delivery (34^0-36^6 weeks) and in women undergoing planned cesarean delivery at 37 or more weeks' gestation. The rate of respiratory distress syndrome with caesarean delivery decreased with increasing gestation, supporting the recommendation to delay planned caesarean delivery until the 39th week. The lack of data on the long term outcomes was the major shortcoming of this meta-analysis, so the long term safety of antenatal corticosteroids at late preterm or term is still not well known.

What this study adds Antenatal steroids administered at 34 or more weeks' gestation reduce the risk of neonatal respiratory morbidity. A single course of corticosteroids can be considered for women at risk of imminent late premature delivery, as well as for women undergoing planned caesarean section at less than 39 weeks' gestation.

Funding, competing interests, data sharing No financial support was received for this study. The authors have no competing interests.
Study registration PROSPERO CRD42016035234.



Forest plot for use of antenatal corticosteroids after 34 weeks' gestation and risk of respiratory distress syndrome



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