All you need to read in the other general medical journals

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Probiotics protect against diarrhoea associated with antibiotics

More evidence that probiotics can help prevent diarrhoea associated with antibiotics has emerged from a meta-analysis of randomised trials. The authors found 82 trials after a systematic search but only 63 reported how many people took the probiotics, how many took the control treatment, and how many developed diarrhoea. Across these 63 trials, probiotics were associated with a 42% reduction in the risk of diarrhoea (relative risk 0.58, 95% CI 0.50 to 0.68; number needed to treat 13, 10.3 to 19.1).

Most trials tested probiotic preparations containing lactobacilli, alone or in mixed cultures. The effect looked consistent in multiple different analyses, including two confined to high quality trials and another that looked specifically at adults taking antibiotics for *Helicobacter pylori* infections (the most commonly reported indication). The authors are confident their results are as robust as they can be given the generally poor quality of the evidence base.

Most trials were underpowered and badly reported. It is still hard to know the precise mix of micro-organisms that is likely to work best and the characteristics of patients most likely to benefit. Details of the antibiotics being taken were missing from many trials, as were reliable assessments of side effects. Still, we have enough encouraging evidence to justify further research to fine tune these results, say the authors. Diarrhoea associated with antibiotics is common and can be life threatening.

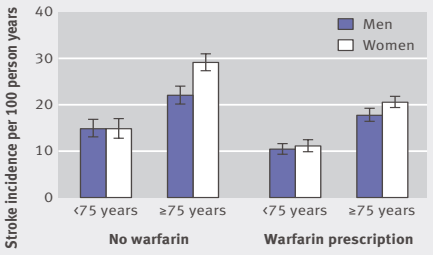
JAMA 2012;307:1959-69

Atrial fibrillation carries a higher risk of stroke for women

Women with atrial fibrillation have a higher risk of ischaemic stroke than men with atrial fibrillation. We still don't know why, but a recent cohort study tells us it has little to do with women being undertreated. In an analysis of claims data from Canada, women filled more prescriptions for warfarin than men in the first month after a hospital admission for atrial fibrillation. And adherence was good in both sexes.

Further analyses linking three administrative databases suggest the sex differential is not due to the different ages or clinical profiles of men and women admitted for atrial fibrillation. After full adjustment for comorbidities, warfarin treatment, and the individual components of the $CHADS_2$ score (congestive heart failure, hypertension, age over 75 years, diabetes mellitus, and previous stroke or transient ischaemic attack), women were still 14% more likely to have an ischaemic stroke than men (2570/44 115 *v* 1696/39 398; hazard ratio 1.14, 95% CI 1.07 to 1.22).

Incidence of stroke in men and women with atrial fibrillation



Adapted from *JAMA* 2012;307:1952-58

The gap between men and women was widest in those aged 75 or over. Women in this age group deserve more attention from stroke prevention researchers, say the authors, particularly those designing trials of newer anticoagulants. We should also develop and test risk scores for stroke that include sex as an independent risk factor.

JAMA 2012;307:1952-8

Vascular biomarkers improved in the clean air over Beijing's Olympics

China's leaders restricted industrial activity and traffic in Beijing during the 2008 Olympic games. The air over the city was significantly cleaner than usual during August and September that year, giving Chinese researchers a window of opportunity to study the impact of air pollution on the vascular physiology of 125 healthy young doctors at one Beijing hospital.

Their study showed that the temporary drop in air pollutants was accompanied by significant improvements in biomarkers of platelet activity and adhesion, including Von Willebrand factor (13% decrease, 95% CI 18.6% to 7.5%) and soluble P selectin (34% decrease, 38.4% to 29.2%). Both bounced back when the restrictions ended and levels of pollutants rose again. Changes in inflammatory biomarkers, blood pressure, and heart rate before, during, and after the Olympics were less consistent, but links between pollutant concentrations and fibrinogen emerged from exploratory analyses.

We know that air pollution damages human health, and this opportunistic study can help us understand why, says a linked editorial (p 2100). The results are consistent with theory that air pollution has prothrombotic effects, particularly the mix prevalent in Beijing, which has very high concentrations of fine particles measuring less than 2.5 µm in diameter. Chinese authorities plan to monitor concentrations of these particles in their major cities from next year, says the editorial. This move is an important advance on current monitoring efforts, which rely on counting "blue sky" days over big cities.

JAMA 2012;307:2068-78

Lenalidomide maintenance for adults with multiple myeloma

Lenalidomide, which is related to thalidomide, is an effective treatment for multiple myeloma when used for induction or treatment of relapse. Three new placebo controlled trials suggest it can also delay progression when used for long term maintenance. Two publicly funded trials tested lenalidomide maintenance after a stem cell transplant. A third, funded by the manufacturer, tested lenalidomide maintenance in older adults who were ineligible for a stem cell transplant. Adults assigned the active treatment had significantly longer progression-free survival than placebo controls in all three trials.

Results for overall survival were mixed, however. Two trials reported no difference, and one reported a significant survival advantage for adults given lenalidomide maintenance after a stem cell transplant (three year survival 88% *v* 80%; hazard ratio 0.62, 95% CI 0.40 to 0.95). Lenalidomide caused the expected haematological side effects in all three trials and a bigger than expected excess of second cancers (7-8% of actively treated adults *v* 3-4% of placebo controls).

The place of this drug in the long term treatment of adults with multiple myeloma is still debatable, says a linked editorial (p 1836). Not least because of the number of extra second cancers associated with treatment, and

"All good science is inspired with the poetry of hope; but, alas, so also is a lot of bad science. If results are negative, then it is a lot easier to hope vainly that they contain hints of great things to come than to admit that years of effort have simply proved nullity."
Read Richard Lehman's journal blog at bmj.com/blogs

remaining doubts about the drug's ability to improve overall survival. In none of the trials were patients questioned about their quality of life.

N Engl J Med 2012;366:1759-69
N Engl J Med 2012;366:1770-81
N Engl J Med 2012;366:1782-91

Lower mortality for countries given US aid to combat HIV

Three quarters of the US government's budget for global health goes to PEPFAR—the President's Emergency Plan for AIDS Relief, launched by George W Bush in 2003. The plan pays for screening, treatment, education, and other elements of modern HIV care in 15 of the world's worst affected countries. In Africa, at least, the investment may have paid off—the nine countries selected for PEPFAR funding had a significantly lower adult mortality between 2004 and 2008 than the 18 countries not selected in a recent analysis of national survey data (adjusted odds ratio 0.84, 95% CI 0.72 to 0.99). The authors estimate that PEPFAR was associated with 740 914 (443 318 to 1 808 601) fewer deaths from all causes and 631 338 (249 026 to 1 060 253) fewer deaths from HIV during the four year study.

These results should reassure observers worried about the unintended consequences of directing such a large proportion of available funding to HIV, say the authors. PEPFAR has clearly done no harm and may have saved many thousands of lives.

An unpopular question remains however, says a linked editorial (p 2097). Could we save even more lives by distributing aid more equitably between HIV and other leading causes of death including pneumonia, diarrhoea, malaria, and birth complications? We don't yet know because the global health community seems reluctant to pit one health intervention directly against another. This is understandable but unethical when resources are finite, says the editorial. And they always are. If it is possible to spend money even more effectively, then we should.

JAMA 2012;307:2060-7

Infectious diseases cause two thirds of child deaths worldwide

The number of children dying before their 5th birthday fell from 9.6 million to 7.6 million in the decade between 2000 and 2010. Slow progress, say researchers, and not nearly enough to meet millennium development goal 4, which asks for a two thirds reduction in child deaths between 1990 and 2015. Their updated estimates of causes of death confirm that infectious diseases were responsible for the greatest proportion of child deaths in 2010 (64.0%, 4.879 million deaths), predominantly pneumonia, diarrhoea, and malaria in children older than 1 month. Two fifths of child deaths that year occurred in neonates (40.3%, 3.072 million deaths). Birth complications, the complications of prematurity, and sepsis or meningitis were the leading causes of death in this age group. Almost half of all child deaths occurred in India, Nigeria, Democratic Republic of the Congo, Pakistan, and China. Less than 3% of all child deaths were medically certified.

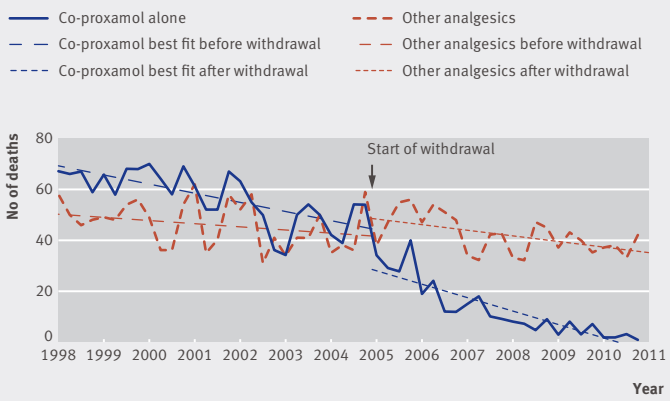
The researchers hope that the latest figures will help target resources and accelerate progress. A linked comment (doi:10.1016/S0140-6736(12)60686-2) hopes that they will lead to a closer look at why these children are dying from preventable diseases and complications; where they are dying; and how the deaths are linked to factors such as poverty, access, and quality of care. Where are the fastest gains being made and how are they being achieved? Only by moving beyond the numbers, however well modelled, can we hope to inform life saving policies in specific countries, it says.

Lancet 2012; doi:10.1016/S0140-6736(12)60560-1

Cite this as: *BMJ* 2012;344:e3359

Deaths from co-proxamol poisoning drop sharply after ban in England and Wales

Deaths from poisoning with co-proxamol and other analgesics



Adapted from *PLoS Med* 2012;9(5):e1001213

In January 2005, the UK's medicines regulator announced the phased withdrawal of co-proxamol, a leading cause of suicide by drug poisoning. In a time series analysis of national statistics from England and Wales, the number of intentional and unintentional deaths involving co-proxamol fell by 62% in the five years after the ban (mean of 40 deaths per quarter before *v* 15 deaths per quarter after; absolute difference −25 deaths, 95% CI −38 to −12). Only 10 deaths involving co-proxamol were recorded as suicide, an open verdict from a coroner's court, or accidental poisoning in 2010. In 1998, 309 such deaths occurred.

Although prescribing of other analgesics increased in the five years after the ruling, numbers of suicides and accidental deaths involving alternative analgesics did not. These analyses included deaths linked to co-codamol, codeine, co-dydramol, dihydrocodeine, non-steroidal anti-inflammatory drugs, paracetamol, and tramadol. The authors are fairly confident that substitution hasn't been a major problem in England and Wales. They weren't able to track trends in deaths caused by morphine, but they did notice a small increase in deaths involving oxycodone—from 2.3 a year between 2001 and 2004, to 8.2 a year between 2005 and 2010.

European, Canadian, and US regulators have since followed the UK's lead. Co-proxamol was withdrawn from the market in all three jurisdictions in 2010.

PLoS Med 2012; doi:10.1371/journal.pmed.1001213