table of contents

WORLD REPORTS

Health crisis worsens in Zimbabwe
Kapp, C.

Margaret Chan’s vision for WHO
Samarasekera, U.

China introduces new rules to deter human organ trade
Watts, J.

US lawmakers tackle safety reforms at the FDA
Zwillich, T.

ARTICLES

Assessment of Swedish snus for tobacco harm reduction: an epidemiological modelling study

Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review
Gilligan, D., Marianne Nicolson, Ian Smith, Harry Groen, Otilia Dalesia, Peter Goldstraw, Matthew Hatton, Penelope Hopwood, Christian Manegold, Franz Schramel, Hans Smit, Jan Van Meerbeeck, Matthew Nankivell and Makesh Parmar DPhil.

Efficacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomised controlled equivalence trial
Hertzen, H.v., Gilda Piaggio, Nguyen Thi My Huong, Karine Arustaman, Evelio Cabezas, Manuel Gomez, Archil Khomassuridze, Rashmi Shah, Suneeta Mittal, Rajasekharan Nair, Radnaabazar Erdenetungalag, To Minh Huong, Nguyen Duc Vy, Nguyen Thi Ngoc Phuong, Hoang Thi Diem Tuyet, and Alexandre Peregoudov.

Improvement of tuberculosis case detection and reduction of discrepancies between men and women by simple sputum-submission instructions: a pragmatic randomised controlled trial
Khan, MS., Osman Dar, Charalambos Sismanidis, Karam Shah, and Peter Godfrey-Faussett.

Hazardous alcohol drinking and premature mortality in Russia: a population based case-control study
Leon, D.A., Lyudmila Saburova, Susannah Tomkins, Evgeny Andreev, Nikolay Kiryanov, Martin McKee, and Vladimir M Shkolnikov.

Prevalence and intensity of Onchocerca volvulus infection and efficacy of ivermectin in endemic communities in Ghana: a two-phase epidemiological study

REVIEW AND OPINION

Vulvovaginal candidosis
Sobel, J.D.

SEMINAR

Amyotrophic lateral sclerosis
Mitchell, J.D.

PUBLIC HEALTH

Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes
Getahun, H., Mark Harrington, Rick O’Brien, and Paul Nunn.
2 years after Operation Drive Out Trash, Zimbabwe is continuing its headlong descent into social and economic collapse, accompanied by increasing human rights abuses. Shortages of doctors, nurses, and medical supplies are crippling the country’s health system. Unemployment is at 80%, inflation topped a dizzying 3700% at the end of April and rises by the day, and there are shortages of everything ranging from electricity to sugar to syringes. The southern African nation has the world’s fourth worst HIV/AIDS rate and what remains of the health system is stricken by a massive exodus of doctors and nurses and industrial action by those who remain. “It can no longer be said the health service is near collapse.

WHO’s new Director-General Margaret Chan has now been in office for 5 months. At the 60th World Health Assembly in May, she announced her refined vision for the global health agency, marking a substantial shift from the priorities of her predecessor. Udani Samarasekera reports. When the late Lee Jong-wook, former Director-General of WHO, took office in July, 2003, he made his priorities clear: HIV/AIDS was topping the agenda at the global health agency. In his first few months he launched his signature issue—the 3 by 5 campaign—which aimed to provide antiretroviral drugs to 3 million people in developing countries by 2005. His successor, Margaret Chan, who took office on Jan 4 this year, has taken a decidedly different approach to putting her stamp on the organisation.

China has introduced a raft of new regulations to try and deter doctors and hospitals from trading in human organs. The move adds strength to an earlier ban on the sale of organs, most of which come from executed prisoners. Jonathan Watts reports from Beijing. The global trade in organs is set for a shake-up after China introduced new penalties for doctors and hospitals that try to profit from the sale of livers, kidneys, hearts, and corneas. Beijing introduced the new regulations last month amid rising international criticism about the country’s mass harvesting of organs from executed prisoners. The new rules issued by the State Council, China’s cabinet, give strength to an earlier ban on the sale of organs, as well as attempting to standardise procedures for transplant surgery. Under the new penalty system for organ traders, doctors will have their licences revoked, hospitals will be suspended from transplant operations for 3 years and officials will be fired. The maximum fines for all involved will be raised to ten times the amount they were set to gain from the business.

Swedish snus is a smokeless tobacco product that has been suggested as a tobacco harm reduction product. Our aim was to assess the potential population health effects of snus in Australia with multistate life tables to estimate the difference in health-adjusted life expectancy between people who have never been smokers and various trajectories of tobacco use, including switching from smoking to snus use; and the potential for net population-level harm given different rates of snus uptake by current smokers, ex-smokers, and people who have never smoked. There was little difference in health-adjusted life expectancy between smokers who quit all tobacco and smokers who switch to snus (difference of 0·1–0·3 years for men and 0·1–0·4 years for women).
For net harm to occur, 14–25 ex-smokers would have to start using snus to offset the health gain from every smoker who switched to snus rather than continuing to smoke. Likewise, 14–25 people who have never smoked would need to start using snus to offset the health gain from every new tobacco user who used snus rather than smoking. Current smokers who switch to using snus rather than continuing to smoke can realise substantial health gains. Snus could produce a net benefit to health at the population level if it is adopted in sufficient numbers by inveterate smokers. Relaxing current restrictions on the sale of snus is more likely to produce a net benefit than harm, with the size of the benefit dependent on how many inveterate smokers switch to snus.


Although surgery offers the best chance of cure for patients with non-small cell lung cancer (NSCLC), the overall 5-year survival rate is modest, and improvements are urgently needed. In the 1990s, much interest was generated from two small trials that reported striking results with neo-adjuvant chemotherapy, and therefore our intergroup randomised trial was designed to investigate whether, in patients with operable non-small cell lung cancer of any stage, outcomes could be improved by giving platinum-based chemotherapy before surgery. Patients were randomised to receive either surgery alone (S), or three cycles of platinum-based chemotherapy followed by surgery (CT-S). Before randomisation, clinicians chose the chemotherapy that would be given from a list of six standard regimens. The primary outcome measure was overall survival, which was analysed on an intention-to-treat basis. 519 patients were randomised (S: 261, CT-S: 258) from 70 centres in the UK, Netherlands, Germany, and Belgium. Most (61%) were clinical stage I, with 31% stage II, and 7% stage III. Neo-adjuvant chemotherapy was feasible (75% of patients received all three cycles of chemotherapy), resulted in a good response rate (49% [95% CI 43%–55%]) and down-staging in 31% (25%–37%) of patients, and did not alter the type or completeness of the surgery (lobectomy: S: 56%, CT-S: 60%, complete resection: S: 80%, CT-S: 82%). Post-operative complications were not increased in the CT-S group, and no impairment of quality of life was observed. However, there was no evidence of a benefit in terms of overall survival (hazard ratio [HR] 1.02, 95% CI 0.80-1.31, p=0.86). Updating the systematic review by addition of the present result suggests a 12% relative survival benefit with the addition of neoadjuvant chemotherapy (1507 patients, HR 0.88, 95% CI 0.76–1.01, p=0.07), equivalent to an absolute improvement in survival of 5% at 5 years. Although there was no evidence of a difference in overall survival with neo-adjuvant chemotherapy, the result is statistically consistent with previous trials, and therefore adds considerable weight to the current evidence.


The most effective route and best interval between several doses of misoprostol to induce abortion have not been defined. Our aim was to assess the effects of the interval between multiple doses of misoprostol and the route of administration to terminate pregnancy. 2066 healthy pregnant women requesting medical abortion with 63 days or less of gestation were randomly assigned within 11 gynaecological centres in six countries to the four treatment groups (three doses of 0.8 mg misoprostol given sublingually at 3-h intervals, vaginally 3 h, sublingually 12 h, and vaginally 12 h), stratifying by gestational age. This was an equivalence trial with a 5% margin of equivalence. The primary endpoints were efficacy of treatment to achieve complete abortion and to terminate pregnancy. The main efficacy analysis excluded women lost to follow-up. Efficacy outcomes were analysed for 2046 women (99%), excluding 20 lost to follow-up. Complete abortion rates at 2-week follow-up were recorded for 431 (84%) in the sublingual and for 434 (85%) women in the vaginal group when misoprostol was given at 3-h intervals (difference 0.4%, 95% CI -0.4 to 4.9, p=0.85 equivalence shown), and for 399 (78%) in the sublingual and for 425 (83%) in the vaginal 12-h groups (4.6%, -0.2 to 9.5, p=0.06, equivalence not shown). In the 3-h groups, pregnancy continued in 29 (6%) women after sublingual and in 20 (4%) women after vaginal administration.
In several settings, women with suspected tuberculosis are less likely to test smear positive than are men. Submission of poor-quality sputum specimens by women might be one reason for the difference between the sexes. We did a pragmatic randomised controlled trial to assess the effect of sputum-submission instructions on female patients. 1494 women and 1561 men with suspected tuberculosis attending the Federal Tuberculosis Centre in Rawalpindi, Pakistan, were randomly assigned between May and July, 2005 either to receive sputum-submission guidance before specimen submission or to submit specimens without specific guidance, according to prevailing practice. Of enrolled patients, 133 (4%) declined to participate. The primary outcome measure was the proportion of instructed and non-instructed women testing smear positive. Intention-to-treat analysis was undertaken on the basis of treatment allocation. This study is registered with the International Standard Randomised Controlled Trial number 34123170. Instructed women were more likely to test smear positive than were controls [Risk ratio 1·63 [95% CI 1·19–2·22]]. Instructions were associated with a higher rate of smear-positive case detection (58 [8%] in controls vs 95 [13%] in the intervention group; p=0·002), a decrease in spot-saliva submission (p=0·003), and an increase in the number of women returning with an early-morning specimen (p=0·02). In men, instructions did not have a significant effect on the proportion testing smear positive or specimen quality. In the Federal Tuberculosis Centre in Rawalpindi, lower smear positivity in women than in men was mainly a function of poor-quality specimen submission. Smear positivity in women was increased substantially by provision of brief instructions. Sputum-submission guidance might be a highly cost-effective intervention to improve smear-positive case detection and reduce the disparity between the sexes in tuberculosis control in low-income countries.


The reason for the low life expectancy in Russian men and large fluctuations in mortality are unknown. We investigated the contribution of alcohol, and hazardous drinking in particular, to male mortality in a typical Russian city. Cases were all deaths in men aged 25–54 years living in Izhevsk occurring between Oct 20, 2003, to Oct 3, 2005. Controls were selected at random from the city population and were frequency matched to deaths by age. Interviews with proxy informants living in the same household as cases were done between Dec 11, 2003, and Nov, 16 2005, and were obtained for 62% (1750/2835) of cases and 57% (1750/3078) of controls. We ascertained frequency and usual amount of beer, wine, and spirits consumed and frequency of consumption of manufactured ethanol-based liquids not intended to be drunk (non-beverage alcohol), and markers of problem drinking. Complete information on markers of problem drinking, frequency of alcohol consumption, education, and smoking was available for 1468 cases and 1496 controls. 751 (51%) cases were classed as problem drinkers or drank non-beverage alcohol, compared with 192 (13%) controls. The mortality odds ratio (OR) for these men, compared with those who either abstained or were non-problematic beverage drinkers, was 6·0 (95% CI 5·0–7·3) after adjustment for smoking and education. The mortality ORs for drinking non-beverage alcohol in the past year (yes vs no) was 9·2 (7·2–11·7) after adjustment for age. Adjustment for volume of ethanol consumed from beverages lowered the OR to 8·3 (6·5–10·7), and further adjustment for education and smoking reduced it to 7·0 (5·5–9·0). A strong direct gradient with mortality was seen for frequency of non-beverage alcohol drinking independent of volume of beverage ethanol consumed. 43% of mortality
was attributable to hazardous drinking (problem drinking or non-beverage alcohol consumption, or both) adjusted for smoking and education. Almost half of all deaths in working age men in a typical Russian city may be accounted for by hazardous drinking. Our analyses provide indirect support for the contention that the sharp fluctuations seen in Russian mortality in the early 1990s could be related to hazardous drinking as indicated by consumption of non-beverage alcohol.


Ivermectin has been used for onchocerciasis control since 1987. Because of the long-term use of this drug and the development of resistance in other nematodes, we have assessed Onchocerca volvulus burdens, effectiveness of ivermectin as a microfilaricide, and its effect on adult female worm reproduction. For the first phase of the study, 2501 individuals in Ghana, from 19 endemic communities who had received six to 18 annual rounds of ivermectin and one ivermectin naive community, were assessed for microfilarial loads 7 days before the 2004 yearly ivermectin treatment, by means of skin snips, and 30 days after treatment to assess the ivermectin microfilaricidal action. For the second phase, skin snips were taken from 342 individuals from ten communities, who were microfilaria positive at pretreatment assessment, on days 90 and 180 after treatment, to identify the effects of ivermectin on female worm fertility, assessed by microfilaria repopulation. 487 (19%) of the 2501 participants were microfilaria positive. The microfilaria prevalence and community microfilarial load in treated communities ranged from 2·2% to 51·8%, and 0·06 microfilariae per snip to 2·85 microfilariae per snip, respectively. Despite treatment, the prevalence rate doubled between 2000 and 2005 in two communities. Microfilaria assessment 30 days after ivermectin treatment showed 100% clearance of microfilaria in more than 99% of people. At day 90 after treatment, four of ten communities had significant microfilaria repopulation, from 7·1% to 21·1% of pretreatment counts, rising to 53·9% by day 180. Ivermectin remains a potent microfilaricide. However, our results suggest that resistant adult parasite populations, which are not responding as expected to ivermectin, are emerging. A high rate of repopulation of skin with microfilariae will allow parasite transmission, possibly with ivermectin-resistant O volvulus, which could eventually lead to recrudescence of the disease.

**REVIEW AND OPINION**

(Since these articles has no abstract, we just provided an extract of the first 100 words of the full text and any section headings)


Despite therapeutic advances, vulvovaginal candidosis remains a common problem worldwide, affecting all strata of society. Understanding of anti-candida host defence mechanisms in the vagina has developed slowly and, despite a growing list of recognised risk factors, a fundamental grasp of pathogenic mechanisms continues to elude us. The absence of rapid, simple, and inexpensive diagnostic tests continues to result in both overdiagnosis and underdiagnosis of vulvovaginal candidosis. I review the epidemiology and pathogenesis of this infection, and also discuss management strategies.

**SEMINAR**


Amyotrophic lateral sclerosis (known in the UK as motor neuron disease) is a devastating illness with uncertain pathogenesis. In this Seminar, we review its natural history, clinical features, diagnostic criteria, variant and mimic syndromes, genetic forms, and epidemiology. Several hypotheses about causes of the disorder are discussed, such as excitotoxicity and oxidant stress, and we review past and present putative disease-modifying treatments. Disease-management strategies, from telling the patient about their illness to end-of-life decisions and palliative care, are presented. We review options for control of the main symptoms of amyotrophic lateral sclerosis—including dysphagia, dysarthria, respiratory distress, pain, and psychological disorders—and care in the terminal phase. The need for good psychosocial and spiritual care of patients and families is emphasised. We conclude with an overview of some current major issues and future prospects, ranging from the search for disease markers to challenging developments such as stem-cell and gene therapy.
PUBLIC HEALTH


The HIV epidemic has led to large increases in the frequency of smear-negative pulmonary tuberculosis, which has poor treatment outcomes and excessive early mortality compared with smear-positive disease. We used a combination of systematic review, document analysis, and global expert opinion to review the extent of this problem. We also looked at policies of national tuberculosis control programmes for the diagnosis of smear-negative pulmonary tuberculosis to assess their coverage, identify the diagnostic difficulties, and find ways to improve the diagnosis of this type of tuberculosis, with a focus on resource-constrained settings with high HIV infection rates. We propose that the internationally recommended algorithm for the diagnosis of smear-negative pulmonary tuberculosis should be revised to include HIV status, severity of AIDS and tuberculosis, and early use of chest radiography in the decision tree. Increased use of promising methods of diagnosis such as sputum liquefaction and concentration and increased availability of fluorescence microscopy should be explored and encouraged. Culturing of sputum in resource-constrained settings with high HIV infection rates should also be encouraged, existing facilities should be made full use of and upgraded, and effective quality-assurance systems should be used. Innovative ways to address human resources issues involved in addressing the diagnostic difficulties are also needed. The development of rapid, simple, and accurate tuberculosis diagnostic tools with applicability at point of care and remote location is essential. To achieve these goals, greater political commitment, scientific interest, and investment are needed.