Bulletin de veille

« Focus sur 12 pathologies graves »

Juillet 2010

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Bulletin de veille – Juillet 2010
« Focus sur 12 pathologies graves »

Ce bulletin de veille est une **publication mensuelle** qui recueille les publications scientifiques autour des **pathologies** suivantes :

- Bronchite chronique obstructive
- Cancer du poumon
- Dengue
- Dépression
- Diabète
- Grippe A
- Maladie d'Alzheimer
- Maladies cardio-vasculaires
- Maladies liées à l'alcool
- Paludisme
- Pathologies liées à l'obésité
- SIDA
- Tuberculose

La recherche documentaire est effectuée dans la **base de données Medline** et porte sur les **12 titres de revues** suivants :

- American journal of epidemiology
- American journal of public health
- BMC public health
- BMJ (Clinical research ed.) - British medical journal
- International journal of epidemiology
- JAMA : the journal of the American Medical Association
- Lancet
- Nature
- Risk analysis : an official publication of the Society for Risk Analysis
- Science
- Social science & medicine
- The New England journal of medicine

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Articles scientifiques issus de l'interrogation de la base **Medline (interrogée le 6/07/2010)**

Rapports , dossiers en ligne et articles supplémentaires

Articles scientifiques

Bronchite chronique obstructive

sommaire

(1) NICHOLAS BL, SKIPP P, BARTON S, SINGH D, *et al.* **Identification of lipocalin and apolipoprotein A1 as biomarkers of chronic obstructive pulmonary disease**. Am J Respir Crit Care Med. 2010 May 15, vol. 181, n° 10, pp.1049-1060
http://dx.doi.org/10.1164/rccm.200906-0857OC

RATIONALE: Much effort is being made to discover noninvasive biomarkers of chronic airway disease that might enable better management, predict prognosis, and provide new therapeutic targets. OBJECTIVES: To undertake a comprehensive, unbiased proteomic analysis of induced sputum and identify novel noninvasive biomarkers for chronic obstructive pulmonary disease (COPD). METHODS: Induced sputum was obtained from patients with COPD with a spectrum of disease severity and from control subjects. Two-dimensional gel electrophoresis and mass spectrometric identification of differentially expressed proteins were first applied to induced sputum from patients with GOLD stage 2 COPD and healthy smoker control subjects. Initial results thus obtained were validated by a combination of immunoassays (Western blotting and ELISA) applied to a large subject cohort. The biomarkers were localized to bronchial mucosa by immunohistochemistry. MEASUREMENTS AND MAIN RESULTS: Of 1,325 individual protein spots identified, 37 were quantitatively and 3 qualitatively different between the two groups ($P < 0.05\%$). Forty protein spots were subjected to tandem mass spectrometry, which identified 15 separate protein species. Seven of these were further quantified in induced sputum from 97 individuals. Using this sequential approach, two of these potential biomarkers (apolipoprotein A1 and lipocalin-1) were found to be significantly reduced in patients with COPD when compared with healthy smokers. Their levels correlated with FEV(1)/FVC, indicating their relationship to disease severity. CONCLUSIONS: A potential role for apolipoprotein A1 and lipocalin-1 in innate defense has been postulated previously; our discovery of their reduction in COPD indicates a deficient innate defense system in airway disease that could explain increased susceptibility to infectious exacerbations

(2) SAHLANDER K, LARSSON K, PALMBERG L. **Altered innate immune response in farmers and smokers**. Innate Immun. 2010 Feb., vol. 16, n° 1, pp.27-38
http://dx.doi.org/10.1177/1753425909106317

Pig farmers and cigarette smokers are continuously exposed to pathogen-associated molecular patterns (PAMPs) have an increased prevalence of respiratory disorders, such as chronic bronchitis and chronic obstructive pulmonary decease (COPD). We hypothesized that markers of innate immunity, T-helper (Th) cell cytokine profile and acute responses to pro-inflammatory stimuli differ between smokers and farmers, who are exposed to organic material on a daily basis and healthy non-exposed subjects. Eleven non-smoking pig farmers, 12 non-farming smokers and 12 controls underwent bronchial lipopolysaccharide (LPS) challenge and exposure in a pig barn during 3 h on separate days. Toll-like receptor 2 (TLR2), TLR4 and CD14 on blood monocytes and neutrophils and intracellular cytokine profile of Th cells were assessed before and 7 h after exposures. The same outcomes were analysed on peripheral blood and purified neutrophils from farmers and controls after stimulation ex vivo with dust from a pig barn and LPS. Circulating neutrophils and IL-13 and IL-4 producing Th cells were increased in smokers and farmers and TLR2 expression on blood monocytes was decreased in farmers compared with controls and smokers. After in vivo exposure, altered TLR expression was only observed in controls and the ex vivo stimulations showed an attenuated response in farmers compared to the control group. The inflammatory systemic response to pro-inflammatory stimuli is altered in farmers and smokers probably because of adaptive mechanisms arising from chronic exposure to organic material. This increased proportion of Th2 cells and reduced TLR2 expression may have health-related implications and may be related to the increased prevalence of respiratory disorders observed in these groups

(3) SETHI S. **Antibiotics in acute exacerbations of chronic bronchitis**. Expert Rev Anti Infect Ther. 2010 Apr., vol. 8, n° 4, pp.405-417
http://dx.doi.org/10.1586/eri.09.133

Acute exacerbations of chronic bronchitis (AECB) are a major contributor to morbidity and mortality in patients with chronic obstructive pulmonary disease, accounting for more than 16 million physician office visits and over 500,000 hospitalizations in the USA each year. Antimicrobials have been recognized by clinical guidelines as an important component in the management of AECB with a bacterial etiology. The challenge of identifying patients most likely to benefit from antimicrobial therapy is difficult in the clinical setting. However, appropriate risk stratification of patients, and the use of antimicrobials within the correct spectrum and for a suitable duration, can improve clinical outcomes while minimizing induction of antimicrobial resistance. With an improved design in pharmacologic and clinical studies, differences can be appreciated among the various antimicrobial agents available to treat AECB. Factors to be considered in antimicrobial agent selection include local tissue penetration, effects on bacteriological eradication, duration of therapy, speed of resolution and prevention or delay of recurrences

Cancer du poumon

sommaire

(1) BARANZINI SE, MUDGE J, VAN VELKINBURGH JC, KHANKHANIAN P, *et al.* **Genome, epigenome and RNA sequences of monozygotic twins discordant for multiple sclerosis**. Nature. 2010 Apr. 29, vol. 464, n° 7293, pp.1351-1356
http://dx.doi.org/10.1038/nature08990 **(accès payant)**

Monozygotic or 'identical' twins have been widely studied to dissect the relative contributions of genetics and environment in human diseases. In multiple sclerosis (MS), an autoimmune demyelinating disease and common cause of neurodegeneration and disability in young adults, disease discordance in monozygotic twins has been interpreted to indicate environmental importance in its pathogenesis. However, genetic and epigenetic differences between monozygotic twins have been described, challenging the accepted experimental model in disambiguating the effects of nature and nurture. Here we report the genome sequences of one MS-discordant monozygotic twin pair, and messenger RNA transcriptome and epigenome sequences of CD4(+) lymphocytes from three MS-discordant, monozygotic twin pairs. No reproducible differences were detected between co-twins among approximately 3.6 million single nucleotide polymorphisms (SNPs) or approximately 0.2 million insertion-deletion polymorphisms. Nor were any reproducible differences observed between siblings of the three twin pairs in HLA haplotypes, confirmed MS-susceptibility SNPs, copy number variations, mRNA and genomic SNP and insertion-deletion genotypes, or the expression of approximately 19,000 genes in CD4(+) T cells. Only 2 to 176 differences in the methylation of approximately 2 million CpG dinucleotides were detected between siblings of the three twin pairs, in contrast to approximately 800 methylation differences between T cells of unrelated individuals and several thousand differences between tissues or between normal and cancerous tissues. In the first systematic effort to estimate sequence variation among monozygotic co-twins, we did not find evidence for genetic, epigenetic or transcriptome differences that explained disease discordance. These are the first, to our knowledge, female, twin and autoimmune disease individual genome sequences reported

(2) CHEN L, YANG S, JAKONCIC J, ZHANG JJ, *et al.* **Migrastatin analogues target fascin to block tumour metastasis**. Nature. 2010 Apr. 15, vol. 464, n° 7291, pp.1062-1066
http://dx.doi.org/10.1038/nature08978 **(accès payant)**

Tumour metastasis is the primary cause of death of cancer patients. Development of new therapeutics preventing tumour metastasis is urgently needed. Migrastatin is a natural product secreted by Streptomyces, and synthesized migrastatin analogues such as macroketone are potent inhibitors of metastatic tumour cell migration, invasion and metastasis. Here we show that these migrastatin analogues target the actin-bundling protein fascin to inhibit its activity. X-ray crystal structural studies reveal that migrastatin analogues bind to one of the actin-binding sites on

fascin. Our data demonstrate that actin cytoskeletal proteins such as fascin can be explored as new molecular targets for cancer treatment, in a similar manner to the microtubule protein tubulin

(3) COLICE GL. **Racial disparities in lung cancer resection**. JAMA. 2010 June 16, vol. 303, n° 23, pp.2411-2412
http://dx.doi.org/10.1001/jama.2010.839 **(accès réservé EHESP)**

(4) CYKERT S, LWORTH-ANDERSON P, MONROE MH, WALKER P, *et al.* **Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer**. JAMA. 2010 June 16, vol. 303, n° 23, pp.2368-2376
http://dx.doi.org/10.1001/jama.2010.79 **(accès réservé EHESP)**

CONTEXT: Lung cancer is the leading cause of cancer death in the United States. Surgical resection for stage I or II non-small cell cancer remains the only reliable treatment for cure. Patients who do not undergo surgery have a median survival of less than 1 year. Despite the survival disadvantage, many patients with early-stage disease do not receive surgical care and rates are even lower for black patients. OBJECTIVES: To identify potentially modifiable factors regarding surgery in patients newly diagnosed with early-stage lung cancer and to explore why blacks undergo surgery less often than whites. DESIGN, SETTING, AND PATIENTS: Prospective cohort study with patients identified by pulmonary, oncology, thoracic surgery, and generalist practices in 5 communities through study referral or computerized tomography review protocol. A total of 437 patients with biopsy-proven or probable early-stage lung cancer were enrolled between December 2005 and December 2008. Before establishment of treatment plans, patients were administered a survey including questions about trust, patient-physician communication, attitudes toward cancer, and functional status. Information about comorbid illnesses was obtained through chart audits. MAIN OUTCOME MEASURE: Lung cancer surgery within 4 months of diagnosis. RESULTS: A total of 386 patients met full eligibility criteria for lung resection surgery. The median age was 66 years (range, 26-90 years) and 29% of patients were black. The surgical rate was 66% for white patients (n = 179/273) compared with 55% for black patients (n = 62/113; P = .05). Negative perceptions of patient-physician communication manifested by a 5-point decrement on a 25-point communication scale (odds ratio [OR], 0.42; 95% confidence interval [CI], 0.32-0.74) and negative perception of 1-year prognosis postsurgery (OR, 0.27; 95% CI, 0.14-0.50; absolute risk, 34%) were associated with decisions against surgery. Surgical rates for blacks were particularly low when they had 2 or more comorbid illnesses (13% vs 62% for <2 comorbidities; OR, 0.04 [95% CI, 0.01-0.25]; absolute risk, 49%) and when blacks lacked a regular source of care (42% with no regular care vs 57% with regular care; OR, 0.20 [95% CI, 0.10-0.43]; absolute risk, 15%). CONCLUSIONS: A decision not to undergo surgery by patients with newly diagnosed lung cancer was independently associated with perceptions of communication and prognosis, older age, multiple comorbidities, and black race. Interventions to optimize surgery should consider these factors

(5) JOHANSSON M, RELTON C, UELAND PM, VOLLSET SE, *et al.* **Serum B vitamin levels and risk of lung cancer**. JAMA. 2010 June 16, vol. 303, n° 23, pp.2377-2385
http://dx.doi.org/10.1001/jama.2010.808 **(accès réservé EHESP)**

CONTEXT: B vitamins and factors related to 1-carbon metabolism help to maintain DNA integrity and regulate gene expression and may affect cancer risk. OBJECTIVE: To investigate if 1-carbon metabolism factors are associated with onset of lung cancer. DESIGN, SETTING, AND PARTICIPANTS: The European Prospective Investigation into Cancer and Nutrition (EPIC) recruited 519,978 participants from 10 countries between 1992 and 2000, of whom 385,747 donated blood. By 2006, 899 lung cancer cases were identified and 1770 control participants were individually matched by country, sex, date of birth, and date of blood collection. Serum levels were measured for 6 factors of 1-carbon metabolism and cotinine. MAIN OUTCOME MEASURE: Odds ratios (ORs) of lung cancer by serum levels of 4 B vitamins (B(2), B(6), folate [B(9)], and B(12)), methionine, and homocysteine. RESULTS: Within the entire EPIC cohort, the age-standardized incidence rates of lung cancer (standardized to the world population, aged 35-79 years) were 6.6, 44.9, and 156.1 per 100,000 person-years among never, former, and current smokers for men,

respectively. The corresponding incidence rates for women were 7.1, 23.9, and 100.9 per 100,000 person-years, respectively. After accounting for smoking, a lower risk for lung cancer was seen for elevated serum levels of B(6) (fourth vs first quartile OR, 0.44; 95% confidence interval [CI], 0.33-0.60; P for trend <.000001), as well as for serum methionine (fourth vs first quartile OR, 0.52; 95% CI, 0.39-0.69; P for trend <.000001). Similar and consistent decreases in risk were observed in never, former, and current smokers, indicating that results were not due to confounding by smoking. The magnitude of risk was also constant with increasing length of follow-up, indicating that the associations were not explained by preclinical disease. A lower risk was also seen for serum folate (fourth vs first quartile OR, 0.68; 95% CI, 0.51-0.90; P for trend = .001), although this was apparent only for former and current smokers. When participants were classified by median levels of serum methionine and B(6), having above-median levels of both was associated with a lower lung cancer risk overall (OR, 0.41; 95% CI, 0.31-0.54), as well as separately among never (OR, 0.36; 95% CI, 0.18-0.72), former (OR, 0.51; 95% CI, 0.34-0.76), and current smokers (OR, 0.42; 95% CI, 0.27-0.65). CONCLUSION: Serum levels of vitamin B(6) and methionine were inversely associated with risk of lung cancer

(6) KATZEFF BS. **Lasofoxifene for postmenopausal women with osteoporosis**. N Engl J Med. 2010 June 10, vol. 362, n° 23, pp.2227-2228
http://www.ncbi.nlm.nih.gov/pubmed/20568309 **(accès réservé EHESP)(accès réservé EHESP)**

(7) LEE W, JIANG Z, LIU J, HAVERTY PM, *et al.* **The mutation spectrum revealed by paired genome sequences from a lung cancer patient**. Nature. 2010 May 27, vol. 465, n° 7297, pp.473-477
http://dx.doi.org/10.1038/nature09004 **(accès payant)**

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small-cell lung carcinomas in smokers being the predominant form of the disease. Although previous studies have identified important common somatic mutations in lung cancers, they have primarily focused on a limited set of genes and have thus provided a constrained view of the mutational spectrum. Recent cancer sequencing efforts have used next-generation sequencing technologies to provide a genome-wide view of mutations in leukaemia, breast cancer and cancer cell lines. Here we present the complete sequences of a primary lung tumour (60x coverage) and adjacent normal tissue (46x). Comparing the two genomes, we identify a wide variety of somatic variations, including >50,000 high-confidence single nucleotide variants. We validated 530 somatic single nucleotide variants in this tumour, including one in the KRAS proto-oncogene and 391 others in coding regions, as well as 43 large-scale structural variations. These constitute a large set of new somatic mutations and yield an estimated 17.7 per megabase genome-wide somatic mutation rate. Notably, we observe a distinct pattern of selection against mutations within expressed genes compared to non-expressed genes and in promoter regions up to 5 kilobases upstream of all protein-coding genes. Furthermore, we observe a higher rate of amino acid-changing mutations in kinase genes. We present a comprehensive view of somatic alterations in a single lung tumour, and provide the first evidence, to our knowledge, of distinct selective pressures present within the tumour environment

(8) MAEMONDO M, INOUE A, KOBAYASHI K, SUGAWARA S, *et al.* **Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR**. N Engl J Med. 2010 June 24, vol. 362, n° 25, pp.2380-2388
http://dx.doi.org/10.1056/NEJMoa0909530 **(accès réservé EHESP)**

BACKGROUND: Non-small-cell lung cancer with sensitive mutations of the epidermal growth factor receptor (EGFR) is highly responsive to EGFR tyrosine kinase inhibitors such as gefitinib, but little is known about how its efficacy and safety profile compares with that of standard chemotherapy. METHODS: We randomly assigned 230 patients with metastatic, non-small-cell lung cancer and EGFR mutations who had not previously received chemotherapy to receive gefitinib or carboplatin-paclitaxel. The primary end point was progression-free survival; secondary end points included overall survival, response rate, and toxic effects. RESULTS: In the planned interim analysis of data for the first 200 patients, progression-free survival was significantly longer

in the gefitinib group than in the standard-chemotherapy group (hazard ratio for death or disease progression with gefitinib, 0.36; P<0.001), resulting in early termination of the study. The gefitinib group had a significantly longer median progression-free survival (10.8 months, vs. 5.4 months in the chemotherapy group; hazard ratio, 0.30; 95% confidence interval, 0.22 to 0.41; P<0.001), as well as a higher response rate (73.7% vs. 30.7%, P<0.001). The median overall survival was 30.5 months in the gefitinib group and 23.6 months in the chemotherapy group (P=0.31). The most common adverse events in the gefitinib group were rash (71.1%) and elevated aminotransferase levels (55.3%), and in the chemotherapy group, neutropenia (77.0%), anemia (64.6%), appetite loss (56.6%), and sensory neuropathy (54.9%). One patient receiving gefitinib died from interstitial lung disease. CONCLUSIONS: First-line gefitinib for patients with advanced non-small-cell lung cancer who were selected on the basis of EGFR mutations improved progression-free survival, with acceptable toxicity, as compared with standard chemotherapy. (UMIN-CTR number, C000000376.)

(9) MURRAY SA, KENDALL M, BOYD K, GRANT L, *et al.* **Archetypal trajectories of social, psychological, and spiritual wellbeing and distress in family care givers of patients with lung cancer: secondary analysis of serial qualitative interviews**. BMJ. 2010, vol. 340, p.c2581
http://www.ncbi.nlm.nih.gov/pubmed/20538635

OBJECTIVE: To assess if family care givers of patients with lung cancer experience the patterns of social, psychological, and spiritual wellbeing and distress typical of the patient, from diagnosis to death. DESIGN: Secondary analysis of serial qualitative interviews carried out every three months for up to a year or to bereavement. SETTING: South east Scotland. PARTICIPANTS: 19 patients with lung cancer and their 19 family carers, totalling 88 interviews (42 with patients and 46 with carers). RESULTS: Carers followed clear patterns of social, psychological, and spiritual wellbeing and distress that mirrored the experiences of those for whom they were caring, with some carers also experiencing deterioration in physical health that impacted on their ability to care. Psychological and spiritual distress were particularly dynamic and commonly experienced. In addition to the "Why us?" response, witnessing suffering triggered personal reflections in carers on the meaning and purpose of life. Certain key time points in the illness tended to be particularly problematic for both carers and patients: at diagnosis, at home after initial treatment, at recurrence, and during the terminal stage. CONCLUSIONS: Family carers witness and share much of the illness experience of the dying patient. The multidimensional experience of distress suffered by patients with lung cancer was reflected in the suffering of their carers in the social, psychological, and spiritual domains, with psychological and spiritual distress being most pronounced. Carers may need to be supported throughout the period of illness not just in the terminal phase and during bereavement, as currently tends to be the case

(10) RUSTHOVEN KE, PUGH TJ. **Stereotactic body radiation therapy for inoperable lung cancer**. JAMA. 2010 June 16, vol. 303, n° 23, pp.2354-2355
http://dx.doi.org/10.1001/jama.2010.777 **(accès réservé EHESP)**

(11) RYAN DP, ENGELMAN JA, FERRONE CR, SAHANI DV, *et al.* **Case records of the Massachusetts General Hospital. Case 19-2010. A 35-year-old man with adenocarcinoma of the cecum** . N Engl J Med. 2010 June 24, vol. 362, n° 25, pp.2411-2419
http://dx.doi.org/10.1056/NEJMcpc1003885 **(accès réservé EHESP)**

Diabète

sommaire

(1) BIGGS ML, MUKAMAL KJ, LUCHSINGER JA, IX JH, *et al.* **Association between adiposity in midlife and older age and risk of diabetes in older adults**. JAMA. 2010 June 23, vol. 303, n° 24, pp.2504-2512
http://dx.doi.org/10.1001/jama.2010.843 **(accès réservé EHESP)**

CONTEXT: Adiposity is a well-recognized risk factor for type 2 diabetes among young and middle-aged adults, but the relationship between body composition and type 2 diabetes is not well

described among older adults. OBJECTIVE: To examine the relationship between adiposity, changes in adiposity, and risk of incident type 2 diabetes in adults 65 years of age and older. DESIGN, SETTING, AND PARTICIPANTS: Prospective cohort study (1989-2007) of 4193 men and women 65 years of age and older in the Cardiovascular Health Study. Measures of adiposity were derived from anthropometry and bioelectrical impedance data at baseline and anthropometry repeated 3 years later. MAIN OUTCOME MEASURE: Incident diabetes was ascertained based on use of antidiabetic medication or a fasting glucose level of 126 mg/dL or greater. RESULTS: Over median follow-up of 12.4 years (range, 0.9-17.8 years), 339 cases of incident diabetes were ascertained (7.1/1000 person-years). The adjusted hazard ratio (HR) (95% confidence interval [CI]) of type 2 diabetes for participants in the highest quintile of baseline measures compared with those in the lowest was 4.3 (95% CI, 2.9-6.5) for body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]), 3.0 (95% CI, 2.0-4.3) for BMI at 50 years of age, 4.2 (95% CI, 2.8-6.4) for weight, 4.0 (95% CI, 2.6-6.0) for fat mass, 4.2 (95% CI, 2.8-6.2) for waist circumference, 2.4 (95% CI, 1.6-3.5) for waist-hip ratio, and 3.8 (95% CI, 2.6-5.5) for waist-height ratio. However, when stratified by age, participants 75 years of age and older had HRs approximately half as large as those 65 to 74 years of age. Compared with weight-stable participants (+/-2 kg), those who gained the most weight from 50 years of age to baseline (> or = 9 kg), and from baseline to the third follow-up visit (> or = 6 kg), had HRs for type 2 diabetes of 2.8 (95% CI, 1.9-4.3) and 2.0 (95% CI, 1.1-3.7), respectively. Participants with a greater than 10-cm increase in waist size from baseline to the third follow-up visit had an HR of type 2 diabetes of 1.7 (95% CI, 1.1-2.8) compared with those who gained or lost 2 cm or less. CONCLUSION: Among older adults, overall and central adiposity, and weight gain during middle age and after the age of 65 years are associated with risk of diabetes

(2) BLUESTONE JA, HEROLD K, EISENBARTH G. **Genetics, pathogenesis and clinical interventions in type 1 diabetes**. Nature. 2010 Apr. 29, vol. 464, n° 7293, pp.1293-1300
http://www.ncbi.nlm.nih.gov/pubmed/20432533 **(accès payant)**

Type 1 diabetes is an autoimmune disorder afflicting millions of people worldwide. Once diagnosed, patients require lifelong insulin treatment and can experience numerous disease-associated complications. The last decade has seen tremendous advances in elucidating the causes and treatment of the disease based on extensive research both in rodent models of spontaneous diabetes and in humans. Integrating these advances has led to the recognition that the balance between regulatory and effector T cells determines disease risk, timing of disease activation, and disease tempo. Here we describe current progress, the challenges ahead and the new interventions that are being tested to address the unmet need for preventative or curative therapies

(3) ELSTAD EA, LUTFEY KE, MARCEAU LD, CAMPBELL SM, *et al.* **What do physicians gain (and lose) with experience? Qualitative results from a cross-national study of diabetes**. Soc Sci Med. 2010 June, vol. 70, n° 11, pp.1728-1736
http://dx.doi.org/10.1016/j.socscimed.2010.02.014 **(accès réservé EHESP)**

An empirical puzzle has emerged over the last several decades of research on variation in clinical decision making involving mixed effects of physician experience. There is some evidence that physicians with greater experience may provide poorer quality care than their less experienced counterparts, as captured by various quality assurance measures. Physician experience is traditionally narrowly defined as years in practice or age, and there is a need for investigation into precisely what happens to physicians as they gain experience, including the reasoning and clinical skills acquired over time and the ways in which physicians consciously implement those skills into their work. In this study, we are concerned with 1) how physicians conceptualize and describe the meaning of their clinical experience, and 2) how they use their experience in clinical practice. To address these questions, we analyzed qualitative data drawn from in-depth interviews with physicians from the United States, United Kingdom, and Germany as a part of a larger factorial experiment of medical decision making for diabetes. Our results show that common measures of physician experience do not fully capture the skills physicians acquire over time or how they implement those skills in their clinical work. We found that what physicians actually gain over time is complex social, behavioral and intuitive wisdom as well as the ability to compare the present

day patient against similar past patients. These active cognitive reasoning processes are essential components of a forward-looking research agenda in the area of physician experience and decision making. Guideline-based outcome measures, accompanied by underdeveloped age- and years-based definitions of experience, may prematurely conclude that more experienced physicians are providing deficient care while overlooking the ways in which they are providing more and better care than their less experienced counterparts

(4) HIRSCH IB, BROWNLEE M. **Beyond hemoglobin A1c--need for additional markers of risk for diabetic microvascular complications**. JAMA. 2010 June 9, vol. 303, n° 22, pp.2291-2292
http://dx.doi.org/10.1001/jama.2010.785 **(accès réservé EHESP)**

(5) LIPPI G, MATTIUZZI C, TARGHER G. **Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults**. N Engl J Med. 2010 May 27, vol. 362, n° 21, p.2030
http://dx.doi.org/10.1056/NEJMc1003829 **(accès réservé EHESP)**

(6) MITKA M. **Critics press FDA to act on evidence of rosiglitazone's cardiac safety issues**. JAMA. 2010 June 16, vol. 303, n° 23, pp.2341-2342
http://dx.doi.org/10.1001/jama.2010.788 **(accès réservé EHESP)**

(7) PALLA L, HIGGINS JP, WAREHAM NJ, SHARP SJ. **Challenges in the use of literature-based meta-analysis to examine gene-environment interactions**. Am J Epidemiol. 2010 June 1, vol. 171, n° 11, pp.1225-1232
http://dx.doi.org/10.1093/aje/kwq051 **(accès réservé EHESP)**

Statistical interactions between genes and environmental exposures with respect to disease outcomes may help to identify biologic mechanisms and pathways and inform behavioral interventions. The number of persons required for a single study to have sufficient statistical power to detect such interactions may be considered prohibitively large, making a meta-analysis of published literature an apparently attractive alternative. However, meta-analysis of gene-environment interactions using published literature is challenging, with the conclusions being likely to suffer from bias and lack of generalizability. The authors highlight these challenges and biases using an illustrative example: meta-analysis of interactions between the Pro12Ala variant of the peroxisome proliferator-activated receptor gamma (PPARgamma) gene and various diet and lifestyle factors in the risk of diabetes. The authors conclude that literature-based meta-analysis conducted to examine gene-environment interactions is unlikely to provide a meaningful quantitative conclusion. Alternative strategies are required, including analyses in scientific consortia established to assess main genetic effects, where individual participant data can be shared, allowing both greater power and consistency of analysis methods. However, these consortia are likely to be limited by lack of standardization of the measures of environmental factors. This issue may ultimately only be resolvable by the de novo establishment of large single or multicenter cohorts using comparable methods

(8) POGACH L, ARON D. **Balancing hypoglycemia and glycemic control: a public health approach for insulin safety**. JAMA. 2010 May 26, vol. 303, n° 20, pp.2076-2077
http://dx.doi.org/10.1001/jama.2010.655 **(accès réservé EHESP)**

(9) SHI Z. **Prevalence of diabetes among men and women in China**. N Engl J Med. 2010 June 24, vol. 362, n° 25, p.2425
http://dx.doi.org/10.1056/NEJMc1004671 **(accès réservé EHESP)**

(10) THANOPOULOU A, KARAMANOS B, ARCHIMANDRITIS A. **Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults**. N Engl J Med. 2010 May 27, vol. 362, n° 21, pp.2030-2031

http://www.ncbi.nlm.nih.gov/pubmed/20518103 **(accès réservé EHESP)(accès réservé EHESP)**

(11) YANG SH, DOU KF, SONG WJ. **Prevalence of diabetes among men and women in China**. N Engl J Med. 2010 June 24, vol. 362, n° 25, pp.2425-2426
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(12) ZARET KS, WHITE MF. **Diabetes forum: Extreme makeover of pancreatic alpha-cells**. Nature. 2010 Apr. 22, vol. 464, n° 7292, pp.1132-1133
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Dépression

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(1)**Postnatal depression: fathers have it too**. Lancet. 2010 May 29, vol. 375, n° 9729, p.1846
http://dx.doi.org/10.1016/S0140-6736(10)60853-7 **(accès réservé EHESP)**

(2) GREENDALE GA, WIGHT RG, HUANG MH, AVIS N, *et al.* **Menopause-associated symptoms and cognitive performance: results from the study of women's health across the nation**. Am J Epidemiol. 2010 June 1, vol. 171, n° 11, pp.1214-1224
http://dx.doi.org/10.1093/aje/kwq067 **(accès réservé EHESP)**

A long-standing, but unproven hypothesis is that menopause symptoms cause cognitive difficulties during the menopause transition. This 6-year longitudinal cohort study of 1,903 midlife US women (2000-2006) asked whether symptoms negatively affect cognitive performance during the menopause transition and whether they are responsible for the negative effect of perimenopause on cognitive processing speed. Major exposures were depressive, anxiety, sleep disturbance, and vasomotor symptoms and menopause transition stages. Outcomes were longitudinal performance in 3 domains: processing speed (Symbol Digit Modalities Test (SDMT)), verbal memory (East Boston Memory Test), and working memory (Digit Span Backward). Adjustment for demographics showed that women with concurrent depressive symptoms scored 1 point lower on the SDMT ($P < 0.05$). On the East Boston Memory Test, the rate of learning among women with anxiety symptoms tested previously was 0.09 smaller per occasion ($P = 0.03$), 53% of the mean learning rate. The SDMT learning rate was 1.00 point smaller during late perimenopause than during premenopause ($P = 0.04$); further adjustment for symptoms did not attenuate this negative effect. Depressive and anxiety symptoms had a small, negative effect on processing speed. The authors found that depressive, anxiety, sleep disturbance, and vasomotor symptoms did not account for the transient decrement in SDMT learning observed during late perimenopause

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http://dx.doi.org/10.1016/j.socscimed.2010.02.005 **(accès réservé EHESP)**

The study examines the mental health consequences of involuntary migration resulting from the world's largest dam project in China. Past claims of a causal link between migration and mental health are inconclusive because they have been based mainly on retrospective data and, therefore, are plagued by a plethora of methodological problems. This study addresses these problems by analyzing the pre- and post-migration changes in depression measured by the CES-D scale with data collected using face-to-face interviews from a sample (n=1530 for the initial survey and 1070 for the follow-up) consisting of both migrants and non-migrants. Changes in CES-D were analyzed using 'the difference model', an analytical strategy which is agreed by methodological experts as "the method of choice" in establishing causal relationship in quasi-experimental research. Our results provide strong support to the claim that forced migration

elevates depression not only directly, but also indirectly by weakening the psychosocial resources that safeguard migrants' mental well-being

(4) LEWIS G. **Mental health of UK Afghan and Iraq veterans**. Lancet. 2010 May 22, vol. 375, n° 9728, pp.1758-1760
http://dx.doi.org/10.1016/S0140-6736(10)60716-7 **(accès réservé EHESP)**

Grippe A

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(1) ABRAHAM T. **The price of poor pandemic communication**. BMJ. 2010, vol. 340, p.c2952
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(2) BAKER MG, THORNLEY CN, MILLS C, ROBERTS S, *et al.* **Transmission of pandemic A/H1N1 2009 influenza on passenger aircraft: retrospective cohort study**. BMJ. 2010, vol. 340, p.c2424
http://www.ncbi.nlm.nih.gov/pubmed/20495017

OBJECTIVES: To assess the risk of transmission of pandemic A/H1N1 2009 influenza (pandemic A/H1N1) from an infected high school group to other passengers on an airline flight and the effectiveness of screening and follow-up of exposed passengers. DESIGN: Retrospective cohort investigation using a questionnaire administered to passengers and laboratory investigation of those with symptoms. SETTING: Auckland, New Zealand, with national and international follow-up of passengers. PARTICIPANTS: Passengers seated in the rear section of a Boeing 747-400 long haul flight that arrived on 25 April 2009, including a group of 24 students and teachers and 97 (out of 102) other passengers in the same section of the plane who agreed to be interviewed. MAIN OUTCOME MEASURES: Laboratory confirmed pandemic A/H1N1 infection in susceptible passengers within 3.2 days of arrival; sensitivity and specificity of influenza symptoms for confirmed infection; and completeness and timeliness of contact tracing. RESULTS: Nine members of the school group were laboratory confirmed cases of pandemic A/H1N1 infection and had symptoms during the flight. Two other passengers developed confirmed pandemic A/H1N1 infection, 12 and 48 hours after the flight. They reported no other potential sources of infection. Their seating was within two rows of infected passengers, implying a risk of infection of about 3.5% for the 57 passengers in those rows. All but one of the confirmed pandemic A/H1N1 infected travellers reported cough, but more complex definitions of influenza cases had relatively low sensitivity. Rigorous follow-up by public health workers located 93% of passengers, but only 52% were contacted within 72 hours of arrival. CONCLUSIONS: A low but measurable risk of transmission of pandemic A/H1N1 exists during modern commercial air travel. This risk is concentrated close to infected passengers with symptoms. Follow-up and screening of exposed passengers is slow and difficult once they have left the airport

(3) BLOOM JD, GONG LI, BALTIMORE D. **Permissive secondary mutations enable the evolution of influenza oseltamivir resistance**. Science. 2010 June 4, vol. 328, n° 5983, pp.1272-1275
http://dx.doi.org/10.1126/science.1187816 **(accès réservé EHESP)**

The His274-->Tyr274 (H274Y) mutation confers oseltamivir resistance on N1 influenza neuraminidase but had long been thought to compromise viral fitness. However, beginning in 2007-2008, viruses containing H274Y rapidly became predominant among human seasonal H1N1 isolates. We show that H274Y decreases the amount of neuraminidase that reaches the cell surface and that this defect can be counteracted by secondary mutations that also restore viral fitness. Two such mutations occurred in seasonal H1N1 shortly before the widespread appearance of H274Y. The evolution of oseltamivir resistance was therefore enabled by "permissive" mutations that allowed the virus to tolerate subsequent occurrences of H274Y. An understanding of this process may provide a basis for predicting the evolution of oseltamivir resistance in other influenza strains

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(6) COHEN D, CARTER P. **Conflicts of interest. WHO and the pandemic flu "conspiracies"**. BMJ. 2010, vol. 340, p.c2912
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http://www.ncbi.nlm.nih.gov/pubmed/20534663

(8) COWLING BJ, CHAN KH, FANG VJ, LAU LL, *et al.* **Comparative epidemiology of pandemic and seasonal influenza A in households**. N Engl J Med. 2010 June 10, vol. 362, n° 23, pp.2175-2184
http://dx.doi.org/10.1056/NEJMoa0911530 **(accès réservé EHESP)**

BACKGROUND: There are few data on the comparative epidemiology and virology of the pandemic 2009 influenza A (H1N1) virus and cocirculating seasonal influenza A viruses in community settings. METHODS: We recruited 348 index patients with acute respiratory illness from 14 outpatient clinics in Hong Kong in July and August 2009. We then prospectively followed household members of 99 patients who tested positive for influenza A virus on rapid diagnostic testing. We collected nasal and throat swabs from all household members at three home visits within 7 days for testing by means of quantitative reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay and viral culture. Using hemagglutination-inhibition and viral-neutralization assays, we tested baseline and convalescent serum samples from a subgroup of patients for antibody responses to the pandemic and seasonal influenza A viruses. RESULTS: Secondary attack rates (as confirmed on RT-PCR assay) among household contacts of index patients were similar for the pandemic influenza virus (8%; 95% confidence interval [CI], 3 to 14) and seasonal influenza viruses (9%; 95% CI, 5 to 15). The patterns of viral shedding and the course of illness among index patients were also similar for the pandemic and seasonal influenza viruses. In a subgroup of patients for whom baseline and convalescent serum samples were available, 36% of household contacts who had serologic evidence of pandemic influenza virus infection did not shed detectable virus or report illness. CONCLUSIONS: Pandemic 2009 H1N1 virus has characteristics that are broadly similar to those of seasonal influenza A viruses in terms of rates of viral shedding, clinical illness, and transmissibility in the household setting

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(10) GODLEE F. **Conflicts of interest and pandemic flu**. BMJ. 2010, vol. 340, p.c2947
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(11) GOLDKIND SF, SAHIN L, GALLAURESI B. **Enrolling pregnant women in research--lessons from the H1N1 influenza pandemic**. N Engl J Med. 2010 June 17, vol. 362, n° 24, pp.2241-2243
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http://dx.doi.org/10.1186/1471-2458-10-322 **(accès libre)**

ABSTRACT: BACKGROUND: Since 2003, Asia-Pacific, particularly Southeast Asia, has received substantial attention because of the anticipation that it could be the epicentre of the next pandemic. There has been active investment but earlier review of pandemic preparedness plans in the region reveals that the translation of these strategic plans into operational plans is still lacking in some countries particularly those with low resources. The objective of this study is to understand the pandemic preparedness programmes, the health systems context, and challenges and constraints specific to the six Asian countries namely Cambodia, Indonesia, Lao PDR, Taiwan, Thailand, and Viet Nam in the prepandemic phase before the start of H1N1/2009. METHODS: The study relied on the Systemic Rapid Assessment toolkit (SYSRA), which evaluates priority disease programmes by taking into account the programmes, the general health system, and the wider socio-cultural and political context. The components under review were: external context; stewardship and organisational arrangements; financing, resource generation and allocation; healthcare provision; and information systems. Qualitative and quantitative data were collected in the second half of 2008 based on a review of published data and interviews with key informants, exploring past and current patterns of health programme and pandemic response. RESULTS: The study shows that health systems in the six countries varied in regard to the epidemiological context, health care financing, and health service provision patterns. For pandemic preparation, all six countries have developed national governance on pandemic preparedness as well as national pandemic influenza preparedness plans and Avian and Human Influenza (AHI) response plans. However, the governance arrangements and the nature of the plans differed. In the five developing countries, the focus was on surveillance and rapid containment of poultry related transmission while preparation for later pandemic stages was limited. The interfaces and linkages between health system contexts and pandemic preparedness programmes in these countries were explored. CONCLUSION: Health system context influences how the six countries have been preparing themselves for a pandemic. At the same time, investment in pandemic preparation in the six Asian countries has contributed to improvement in health system surveillance, laboratory capacity, monitoring and evaluation and public communications. A number of suggestions for improvement were presented to strengthen the pandemic preparation and mitigation as well as to overcome some of the underlying health system constraints

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http://dx.doi.org/10.1126/science.1190994 **(accès réservé EHESP)**

(14) KIRBY T. **Jim Bishop: the Chief Medical Officer of Australia**. Lancet. 2010 May 1, vol. 375, n° 9725, p.1517
http://dx.doi.org/10.1016/S0140-6736(10)60645-9 **(accès réservé EHESP)**

(15) LEE VJ, YAP J, COOK AR, CHEN MI, *et al.* **Oseltamivir ring prophylaxis for containment of 2009 H1N1 influenza outbreaks**. N Engl J Med. 2010 June 10, vol. 362, n° 23, pp.2166-2174
http://dx.doi.org/10.1056/NEJMoa0908482 **(accès réservé EHESP)**

BACKGROUND: From June 22 through June 25, 2009, four outbreaks of infection with the pandemic influenza A (H1N1) virus occurred in Singapore military camps. We report the efficacy of ring chemoprophylaxis (geographically targeted containment by means of prophylaxis) with oseltamivir to control outbreaks of 2009 H1N1 influenza in semiclosed environments. METHODS: All personnel with suspected infection were tested and clinically isolated if infection was

confirmed. In addition, we administered postexposure ring chemoprophylaxis with oseltamivir and segregated the affected military units to contain the spread of the virus. All personnel were screened three times weekly both for virologic infection, by means of nasopharyngeal swabs and reverse-transcriptase-polymerase-chain-reaction assay with sequencing, and for clinical symptoms, by means of questionnaires. RESULTS: A total of 1175 personnel were at risk across the four sites, with 1100 receiving oseltamivir prophylaxis. A total of 75 personnel (6.4%) were infected before the intervention, and 7 (0.6%) after the intervention. There was a significant reduction in the overall reproductive number (the number of new cases attributable to the index case), from 1.91 (95% credible interval, 1.50 to 2.36) before the intervention to 0.11 (95% credible interval, 0.05 to 0.20) after the intervention. Three of the four outbreaks showed a significant reduction in the rate of infection after the intervention. Molecular analysis revealed that all four outbreaks were derived from the New York lineage of the 2009 H1N1 virus and that cases within each outbreak were due to transmission rather than unrelated episodes of infection. Of the 816 personnel treated with oseltamivir who were surveyed, 63 (7.7%) reported mild, nonrespiratory side effects of the drug, with no severe adverse events. CONCLUSIONS: Oseltamivir ring chemoprophylaxis, together with prompt identification and isolation of infected personnel, was effective in reducing the impact of outbreaks of 2009 H1N1 influenza in semiclosed settings

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http://www.ncbi.nlm.nih.gov/pubmed/20530069

(17) STEELFISHER GK, BLENDON RJ, BEKHEIT MM, LUBELL K. **The public's response to the 2009 H1N1 influenza pandemic**. N Engl J Med. 2010 June 3, vol. 362, n° 22, p.e65
http://dx.doi.org/NEJMp1005102 [pii];10.1056/NEJMp1005102 **(accès réservé EHESP)**

(18) SUESS T, BUCHHOLZ U, DUPKE S, GRUNOW R, *et al.* **Shedding and transmission of novel influenza virus A/H1N1 infection in households--Germany, 2009**. Am J Epidemiol. 2010 June 1, vol. 171, n° 11, pp.1157-1164
http://dx.doi.org/10.1093/aje/kwq071 **(accès réservé EHESP)**

Essential epidemiologic and virologic parameters must be measured to provide evidence for policy/public health recommendations and mathematical modeling concerning novel influenza A/H1N1 virus (NIV) infections. Therefore, from April through August of 2009, the authors collected nasopharyngeal specimens and information on antiviral medication and symptoms from households with NIV infection on a daily basis in Germany. Specimens were analyzed quantitatively by using reverse transcriptase-polymerase chain reaction. In 36 households with 83 household contacts, 15 household contacts became laboratory-confirmed secondary cases of NIV. Among 47 contacts without antiviral prophylaxis, 12 became cases (secondary attack rate of 26%), and 1 (8%) of these was asymptomatic. The mean and median serial interval were 2.6 and 3 days, respectively (range: 1-3 days). On average, the authors detected viral RNA copies for 6.6 illness days (treated in time = 5.7 days, not treated in time = 7.1 days; P = 0.06), but they estimated that most patients cease to excrete viable virus by the fifth illness day. Shedding profiles were consistent with the number and severity of symptoms. Compared with other nasopharyngeal specimen types, nasal wash was the most sensitive. These results support the notion that epidemiologic and virologic characteristics of NIV are in many aspects similar to those of seasonal influenza

(19) UYEKI TM. **2009 H1N1 virus transmission and outbreaks**. N Engl J Med. 2010 June 10, vol. 362, n° 23, pp.2221-2223
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http://dx.doi.org/10.1126/science.1189132 **(accès réservé EHESP)**

The emergence of pandemic H1N1/2009 influenza demonstrated that pandemic viruses could be generated in swine. Subsequent reintroduction of H1N1/2009 to swine has occurred in multiple countries. Through systematic surveillance of influenza viruses in swine from a Hong Kong abattoir, we characterize a reassortant progeny of H1N1/2009 with swine viruses. Swine experimentally infected with this reassortant developed mild illness and transmitted infection to contact animals. Continued reassortment of H1N1/2009 with swine influenza viruses could produce variants with transmissibility and altered virulence for humans. Global systematic surveillance of influenza viruses in swine is warranted

(21) WADDINGTON CS, WALKER WT, OESER C, REINER A, *et al.* **Safety and immunogenicity of AS03B adjuvanted split virion versus non-adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomised, parallel group, multicentre study**. BMJ. 2010, vol. 340, p.c2649
http://www.ncbi.nlm.nih.gov/pubmed/20508026

OBJECTIVES: To compare the safety, reactogenicity, and immunogenicity of an adjuvanted split virion H1N1 vaccine and a non-adjuvanted whole virion vaccine used in the pandemic immunisation programme in the United Kingdom. DESIGN: Open label, randomised, parallel group, phase II study. SETTING: Five UK centres (Oxford, Southampton, Bristol, Exeter, and London). PARTICIPANTS: Children aged 6 months to less than 13 years for whom a parent or guardian had provided written informed consent and who were able to comply with study procedures were eligible. Those with laboratory confirmed pandemic H1N1 influenza or clinically diagnosed disease meriting antiviral treatment, allergy to egg or any other vaccine components, or coagulation defects, or who were severely immunocompromised or had recently received blood products were excluded. Children were grouped by age: 6 months-<3 years (younger group) and 3-<13 years (older group). Recruitment was by media advertising and direct mailing. Recruitment visits were attended by 949 participants, of whom 943 were enrolled and 937 included in the per protocol analysis. INTERVENTIONS: Participants were randomised 1:1 to receive AS03(B) (tocopherol based oil in water emulsion) adjuvanted split virion vaccine derived from egg culture or non-adjuvanted whole virion vaccine derived from cell culture. Both were given as two doses 21 days apart. Reactogenicity data were collected for one week after immunisation by diary card. Serum samples were collected at baseline and after the second dose. MAIN OUTCOME MEASURES: Primary reactogenicity end points were frequency and severity of fever, tenderness, swelling, and erythema after vaccination. Immunogenicity was measured by microneutralisation and haemagglutination inhibition assays. The primary immunogenicity objective was a comparison between vaccines of the percentage of participants showing seroconversion by the microneutralisation assay (fourfold rise to a titre of >or=1:40 from before vaccination to three weeks after the second dose). RESULTS: Seroconversion rates were higher after the adjuvanted split virion vaccine than after the whole virion vaccine, most notably in the youngest children (163 of 166 participants with paired serum samples (98.2%, 95% confidence interval 94.8% to 99.6%) v 157 of 196 (80.1%, 73.8% to 85.5%), P<0.001) in children under 3 years and 226 of 228 (99.1%, 96.9% to 99.9%) v 95.9%, 92.4% to 98.1%, P=0.03) in those over 3 years). The adjuvanted split virion vaccine was more reactogenic than the whole virion vaccine, with more frequent systemic reactions and severe local reactions in children aged over 5 years after dose one (13 (7.2%, 3.9% to 12%) v 2 (1.1%, 0.1% to 3.9%), P<0.001) and dose two (15 (8.5%, 4.8% to 13.7%) v 2 (1.1%, 0.1% to 4.1%), P<0.002) and after dose two in those under 5 years (15 (5.9%, 3.3% to 9.6%) v 0 (0.0%, 0% to 1.4%), P<0.001). Dose two of the adjuvanted split virion vaccine was more reactogenic than dose one, especially for fever >or=38 masculineC in those aged under 5 (24 (8.9%, 5.8% to 12.9%) v 57 (22.4%, 17.5% to 28.1%), P<0.001). CONCLUSIONS: In this first direct comparison of an AS03(B) adjuvanted split virion versus whole virion non-adjuvanted H1N1 vaccine, the adjuvanted vaccine, while more reactogenic, was more immunogenic and, importantly, achieved high seroconversion rates in children aged less than 3 years. This indicates the potential for improved immunogenicity of influenza vaccines in this age group. TRIAL REGISTRATION: Clinical trials.gov NCT00980850; ISRCTN89141709

(22) ZAROCOSTAS J. **Swine flu pandemic review panel seeks access to confidential documents between WHO and drug companies**. BMJ. 2010, vol. 340, p.c2792

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Maladies d'Alzheimer

sommaire

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http://dx.doi.org/10.1001/jama.2010.802 **(accès réservé EHESP)**

(2) KAMEROW D. **What I learnt from Mom**. BMJ. 2010, vol. 340, p.c2973
http://www.ncbi.nlm.nih.gov/pubmed/20530558

(3) MAYEUX R. **Clinical practice. Early Alzheimer's disease**. N Engl J Med. 2010 June 10, vol. 362, n° 23, pp.2194-2201
http://dx.doi.org/10.1056/NEJMcp0910236 **(accès réservé EHESP)**

(4) NOURHASHEMI F, ANDRIEU S, GILLETTE-GUYONNET S, GIRAUDEAU B, *et al.* **Effectiveness of a specific care plan in patients with Alzheimer's disease: cluster randomised trial (PLASA study)**. BMJ. 2010, vol. 340, p.c2466
http://www.ncbi.nlm.nih.gov/pubmed/20522656

OBJECTIVE: To test the effectiveness of a comprehensive specific care plan in decreasing the rate of functional decline in patients with mild to moderate Alzheimer's disease compared with usual care in memory clinics. DESIGN: Cluster randomised trial. SETTING: 50 memory clinics in France. PARTICIPANTS: Patients with Alzheimer's disease (mini-mental state examination score 12-26). 1131 patients were included: 574 from 26 clinics in the intervention group, and 557 from 24 clinics in the usual care (control) group. Memory clinics were the unit of randomisation. INTERVENTION: The intervention included a comprehensive standardised twice yearly consultation for patients and their caregivers, with standardised guidelines for the management of problems identified during the assessment. MAIN OUTCOME MEASURES: The primary outcome measure was change on the Alzheimer's Disease Cooperative Study-activities of daily living scale assessed at 12 and 24 months. Secondary outcome measures were the rate of admission to institutional care and mortality. RESULTS: At two years the assessment was completed by 58.4% (n=335) of patients in the intervention group and 61.6% (n=343) in the control group. The rate of functional decline at two years did not differ between the groups. The annual rate of change on the Alzheimer's Disease Cooperative Study-activities of daily living was estimated at -5.73 (95% confidence interval -6.89 to -4.57) in the intervention group and -5.96 (-7.05 to -4.86) in the control group (P=0.78). CONCLUSION: A comprehensive specific care plan in memory clinics had no additional positive effect on functional decline in patients with mild to moderate Alzheimer's disease. Future research should aim to determine the effects of more direct involvement of general practitioners. TRIAL REGISTRATION: ClinicalTrials.gov NCT00480220

(5) SCHNEIDER LS. **Care plans for people with Alzheimer's disease**. BMJ. 2010, vol. 340, p.c2626
http://www.ncbi.nlm.nih.gov/pubmed/20522658

(6) VOELKER R. **Effective prevention remains elusive for cognitive decline and dementia**. JAMA. 2010 June 23, vol. 303, n° 24, p.2462
http://dx.doi.org/10.1001/jama.2010.832 **(accès réservé EHESP)**

Maladies cardio-vasculaires

sommaire

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http://dx.doi.org/10.1126/science.328.5983.1220 **(accès réservé EHESP)**

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http://dx.doi.org/10.1093/aje/kwq082 **(accès réservé EHESP)**

Estimating risk of intracranial hemorrhage (ICH) for patients with unruptured brain arteriovenous malformations (AVMs) in the natural course is essential for assessing risks and benefits of treatment. Traditionally, the survival period starts at the time of diagnosis and ends at ICH, but most patients are quickly censored because of treatment. Alternatively, a survival period from birth to first ICH, censoring at the date of diagnosis, has been proposed. The authors quantitatively compared these 2 timelines using survival analysis in 1,581 Northern California brain AVM patients (2000-2007). Time-shift analysis of the birth-to-diagnosis timeline and maximum pseudolikelihood identified the point at which the 2 survival curves overlapped; the 95% confidence interval was determined using bootstrapping. Annual ICH rates per 100 patient-years were similar for both the birth-to-diagnosis (1.27, 95% confidence interval (CI): 1.18, 1.36) and the diagnosis-to-ICH (1.17, 95% CI: 0.89, 1.53) timelines, despite differences in curve morphology. Shifting the birth-to-diagnosis timeline an optimal amount (10.3 years, 95% CI: 3.3, 17.4) resulted in similar ICH survival curves (P = 0.979). These results suggest that the unconventional birth-to-diagnosis approach can be used to analyze risk factors for natural history risk in unruptured brain AVM patients, providing greater statistical power. The data also suggest a biologic change around age 10 years influencing ICH rate

(5) KIMURA K, SAKAI-KIMURA M, TAKAHASHI R, WATANABE A, *et al.* **Too friable to treat?** Lancet. 2010 May 1, vol. 375, n° 9725, p.1578
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http://dx.doi.org/10.1016/S0140-6736(10)60448-5 **(accès réservé EHESP)**

(7) RENOUX C, DELL'ANIELLO S, GARBE E, SUISSA S. **Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study**. BMJ. 2010, vol. 340, p.c2519
http://www.ncbi.nlm.nih.gov/pubmed/20525678

OBJECTIVES: To determine the risk of stroke associated with oral and transdermal routes of administration of hormone replacement therapy. DESIGN: Population based nested case-control study. Setting About 400 general practices in the United Kingdom contributing to the General Practice Research Database. Participants Cohort of all women in the database aged 50-79 years between 1 January 1987 and 31 October 2006 who were members of a practice that fulfilled predefined quality criteria and without a diagnosis of stroke before cohort entry. For each case of stroke occurring during follow-up, up to four controls were selected from among the cohort members in the risk sets defined by the case. Exposure to hormone replacement therapy (HRT)

was categorised into oestrogens only, oestrogens plus progestogen, progestogen only, and tibolone. Oestrogens were further subdivided according to the route of administration (oral v transdermal) and dose (high v low). Main outcome measures Rate ratio of stroke associated with current use of oral and transdermal HRT compared with no use. Current use was considered as a prescription whose duration included the index date. RESULTS: There were 15,710 cases of stroke matched to 59 958 controls. The rate of stroke in the cohort was 2.85 per 1000 per year. The adjusted rate ratio of stroke associated with current use of transdermal HRT was 0.95 (95% CI 0.75 to 1.20) relative to no use. The risk of stroke was not increased with use of low oestrogen dose patches (rate ratio 0.81(0.62 to 1.05)) compared with no use, whereas the risk was increased with high dose patches (rate ratio 1.89 (1.15 to 3.11)). Current users of oral HRT had a higher rate of stroke than non-users (rate ratio 1.28 (1.15 to 1.42)) with both low dose and high dose. CONCLUSIONS: The use of transdermal HRT containing low doses of oestrogen does not seem to increase the risk of stroke. The presence of residual confounding, however, cannot be entirely excluded in the interpretation of this finding

(8) ROSENSON RS. **Lp-PLA(2) and risk of atherosclerotic vascular disease**. Lancet. 2010 May 1, vol. 375, n° 9725, pp.1498-1500
http://dx.doi.org/10.1016/S0140-6736(10)60488-6 **(accès réservé EHESP)**

(9) RUNCHEY S, MCGEE S. **Does this patient have a hemorrhagic stroke?: clinical findings distinguishing hemorrhagic stroke from ischemic stroke**. JAMA. 2010 June 9, vol. 303, n° 22, pp.2280-2286
http://dx.doi.org/10.1001/jama.2010.754 **(accès réservé EHESP)**

CONTEXT: The 2 fundamental subtypes of stroke are hemorrhagic stroke and ischemic stroke. Although neuroimaging is required to distinguish these subtypes, the diagnostic accuracy of bedside findings has not been systematically reviewed. OBJECTIVE: To determine the accuracy of clinical examination in distinguishing hemorrhagic stroke from ischemic stroke. DATA SOURCES: MEDLINE and EMBASE searches of English-language articles published from January 1966 to April 2010. STUDY SELECTION: Prospective studies of adult patients with stroke that compared initial clinical findings with accepted diagnostic standards of hemorrhagic stroke (computed tomography or autopsy). DATA EXTRACTION: Both authors independently appraised study quality and extracted relevant data. DATA SYNTHESIS: Nineteen prospective studies meeting inclusion criteria were identified (N = 6438 patients; n = 1528 [24%] with hemorrhage stroke). Several findings significantly increase the probability of hemorrhagic stroke: coma (likelihood ratio [LR], 6.2; 95% confidence interval [CI], 3.2-12), neck stiffness (LR, 5.0; 95% CI, 1.9-12.8), seizures accompanying the neurologic deficit (LR, 4.7; 95% CI, 1.6-14), diastolic blood pressure greater than 110 mm Hg (LR, 4.3; 95% CI, 1.4-14), vomiting (LR, 3.0; 95% CI, 1.7-5.5), and headache (LR, 2.9; 95% CI, 1.7-4.8). Other findings decrease the probability of hemorrhage: cervical bruit (LR, 0.12; 95% CI, 0.03-0.47) and prior transient ischemic attack (LR, 0.34; 95% CI, 0.18-0.65). A Siriraj score greater than 1 increases the probability of hemorrhage (LR, 5.7; 95% CI, 4.4-7.4) while a score lower than -1 decreases the probability (LR, 0.29; 95% CI, 0.23-0.37). Nonetheless, many patients with stroke lack any diagnostic finding, and 20% have Siriraj scores between 1 and -1, which are diagnostically unhelpful (LR, 0.94; 95% CI, 0.77-1.1). CONCLUSION: In patients with acute stroke, certain findings accurately increase or decrease the probability of intracranial hemorrhage, but no finding or combination of findings is definitively diagnostic in all patients, and diagnostic certainty requires neuroimaging

(10) SMITH LN, JAMES R, BARBER M, RAMSAY S, *et al.* **Rehabilitation of patients with stroke: summary of SIGN guidance**. BMJ. 2010, vol. 340, p.c2845
http://www.ncbi.nlm.nih.gov/pubmed/20551122

(11) TANNE JH. **GlaxoSmithKline denies it has settled thousands of lawsuits over rosiglitazone (Avandia)**. BMJ. 2010, vol. 340, p.c3010
http://www.ncbi.nlm.nih.gov/pubmed/20530068

(12) THOMPSON A, GAO P, ORFEI L, WATSON S, *et al.* **Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies**. Lancet. 2010 May 1, vol. 375, n° 9725, pp.1536-1544
http://dx.doi.org/10.1016/S0140-6736(10)60319-4 **(accès réservé EHESP)**

BACKGROUND: Lipoprotein-associated phospholipase A(2) (Lp-PLA(2)), an inflammatory enzyme expressed in atherosclerotic plaques, is a therapeutic target being assessed in trials of vascular disease prevention. We investigated associations of circulating Lp-PLA(2) mass and activity with risk of coronary heart disease, stroke, and mortality under different circumstances. METHODS: With use of individual records from 79 036 participants in 32 prospective studies (yielding 17 722 incident fatal or non-fatal outcomes during 474 976 person-years at risk), we did a meta-analysis of within-study regressions to calculate risk ratios (RRs) per 1 SD higher value of Lp-PLA(2) or other risk factor. The primary outcome was coronary heart disease. FINDINGS: Lp-PLA(2) activity and mass were associated with each other (r=0.51, 95% CI 0.47-0.56) and proatherogenic lipids. We noted roughly log-linear associations of Lp-PLA(2) activity and mass with risk of coronary heart disease and vascular death. RRs, adjusted for conventional risk factors, were: 1.10 (95% CI 1.05-1.16) with Lp-PLA(2) activity and 1.11 (1.07-1.16) with Lp-PLA(2) mass for coronary heart disease; 1.08 (0.97-1.20) and 1.14 (1.02-1.27) for ischaemic stroke; 1.16 (1.09-1.24) and 1.13 (1.05-1.22) for vascular mortality; and 1.10 (1.04-1.17) and 1.10 (1.03-1.18) for non-vascular mortality, respectively. RRs with Lp-PLA(2) did not differ significantly in people with and without initial stable vascular disease, apart from for vascular death with Lp-PLA(2) mass. Adjusted RRs for coronary heart disease were 1.10 (1.02-1.18) with non-HDL cholesterol and 1.10 (1.00-1.21) with systolic blood pressure. INTERPRETATION: Lp-PLA(2) activity and mass each show continuous associations with risk of coronary heart disease, similar in magnitude to that with non-HDL cholesterol or systolic blood pressure in this population. Associations of Lp-PLA(2) mass and activity are not exclusive to vascular outcomes, and the vascular associations depend at least partly on lipids. FUNDING: UK Medical Research Council, GlaxoSmithKline, and British Heart Foundation

(13) TORPY JM, BURKE AE, GLASS RM. **JAMA patient page. Hemorrhagic stroke**. JAMA. 2010 June 9, vol. 303, n° 22, p.2312
http://dx.doi.org/10.1001/jama.303.22.2312 **(accès réservé EHESP)**

Maladies liées à l'alcool

sommaire

(1) AGRAWAL K, CERTAIN M. **Images in clinical medicine. Visible peristalsis**. N Engl J Med. 2010 June 17, vol. 362, n° 24, p.e68
http://dx.doi.org/10.1056/NEJMicm0910079 **(accès réservé EHESP)**

(2) FEAR NT, JONES M, MURPHY D, HULL L, *et al.* **What are the consequences of deployment to Iraq and Afghanistan on the mental health of the UK armed forces? A cohort study**. Lancet. 2010 May 22, vol. 375, n° 9728, pp.1783-1797
http://dx.doi.org/10.1016/S0140-6736(10)60672-1 **(accès réservé EHESP)**

BACKGROUND: Concerns have been raised about the psychological effect of continued combat exposure and of repeated deployments. We examined the consequences of deployment to Iraq and Afghanistan on the mental health of UK armed forces from 2003 to 2009, the effect of multiple deployments, and time since return from deployment. METHODS: We reassessed the prevalence of probable mental disorders in participants of our previous study (2003-05). We also studied two new randomly chosen samples: those with recent deployment to Afghanistan, and those who had joined the UK armed forces since April, 2003, to ensure that the final sample continued to be representative of the UK armed forces. Between November, 2007, and September, 2009, participants completed a questionnaire about their deployment experiences and health outcomes. FINDINGS: 9990 (56%) participants completed the study questionnaire (8278 regulars, 1712 reservists). The prevalence of probable post-traumatic stress disorder was 4.0% (95% CI 3.5-4.5; n=376), 19.7% (18.7-20.6; n=1908) for symptoms of common mental disorders, and 13.0% (12.2-

13.8; n=1323) for alcohol misuse. Deployment to Iraq or Afghanistan was significantly associated with alcohol misuse for regulars (odds ratio 1.22, 95% CI 1.02-1.46) and with probable post-traumatic stress disorder for reservists (2.83, 1.23-6.51). Regular personnel in combat roles were more likely than were those in support roles to report probable post-traumatic stress disorder (1.87, 1.26-2.78). There was no association with number of deployments for any outcome. There was some evidence for a small increase in the reporting of probable post-traumatic stress disorder with time since return from deployment in regulars (1.13, 1.03-1.24). INTERPRETATION: Symptoms of common mental disorders and alcohol misuse remain the most frequently reported mental disorders in UK armed forces personnel, whereas the prevalence of probable post-traumatic stress disorder was low. These findings show the importance of continued health surveillance of UK military personnel. FUNDING: UK Ministry of Defence

(3) LEWIS G. **Mental health of UK Afghan and Iraq veterans**. Lancet. 2010 May 22, vol. 375, n° 9728, pp.1758-1760
http://dx.doi.org/10.1016/S0140-6736(10)60716-7 **(accès réservé EHESP)**

(4) SPURGEON D. **Alcohol and drug misuse is taking a "daily toll" on US adolescents**. BMJ. 2010, vol. 340, p.c3035
http://www.ncbi.nlm.nih.gov/pubmed/20530559

(5) SWAIN S, KRAUSE T, LARAMEE P, STEWART S. **Diagnosis and clinical management of alcohol related physical complications: summary of NICE guidance**. BMJ. 2010, vol. 340, p.c2942
http://www.ncbi.nlm.nih.gov/pubmed/20554661

Paludisme

sommaire

(1) FIDOCK DA. **Drug discovery: Priming the antimalarial pipeline**. Nature. 2010 May 20, vol. 465, n° 7296, pp.297-298
http://dx.doi.org/10.1038/465297a **(accès payant)**

(2) GAMO FJ, SANZ LM, VIDAL J, DE CC, *et al.* **Thousands of chemical starting points for antimalarial lead identification**. Nature. 2010 May 20, vol. 465, n° 7296, pp.305-310
http://dx.doi.org/10.1038/nature09107 **(accès payant)**

Malaria is a devastating infection caused by protozoa of the genus Plasmodium. Drug resistance is widespread, no new chemical class of antimalarials has been introduced into clinical practice since 1996 and there is a recent rise of parasite strains with reduced sensitivity to the newest drugs. We screened nearly 2 million compounds in GlaxoSmithKline's chemical library for inhibitors of P. falciparum, of which 13,533 were confirmed to inhibit parasite growth by at least 80% at 2 microM concentration. More than 8,000 also showed potent activity against the multidrug resistant strain Dd2. Most (82%) compounds originate from internal company projects and are new to the malaria community. Analyses using historic assay data suggest several novel mechanisms of antimalarial action, such as inhibition of protein kinases and host-pathogen interaction related targets. Chemical structures and associated data are hereby made public to encourage additional drug lead identification efforts and further research into this disease

(3) GETHING PW, SMITH DL, PATIL AP, TATEM AJ, *et al.* **Climate change and the global malaria recession**. Nature. 2010 May 20, vol. 465, n° 7296, pp.342-345
http://dx.doi.org/10.1038/nature09098 **(accès payant)**

The current and potential future impact of climate change on malaria is of major public health interest. The proposed effects of rising global temperatures on the future spread and intensification of the disease, and on existing malaria morbidity and mortality rates, substantively

influence global health policy. The contemporary spatial limits of Plasmodium falciparum malaria and its endemicity within this range, when compared with comparable historical maps, offer unique insights into the changing global epidemiology of malaria over the last century. It has long been known that the range of malaria has contracted through a century of economic development and disease control. Here, for the first time, we quantify this contraction and the global decreases in malaria endemicity since approximately 1900. We compare the magnitude of these changes to the size of effects on malaria endemicity proposed under future climate scenarios and associated with widely used public health interventions. Our findings have two key and often ignored implications with respect to climate change and malaria. First, widespread claims that rising mean temperatures have already led to increases in worldwide malaria morbidity and mortality are largely at odds with observed decreasing global trends in both its endemicity and geographic extent. Second, the proposed future effects of rising temperatures on endemicity are at least one order of magnitude smaller than changes observed since about 1900 and up to two orders of magnitude smaller than those that can be achieved by the effective scale-up of key control measures. Predictions of an intensification of malaria in a warmer world, based on extrapolated empirical relationships or biological mechanisms, must be set against a context of a century of warming that has seen marked global declines in the disease and a substantial weakening of the global correlation between malaria endemicity and climate

(4) GUIGUEMDE WA, SHELAT AA, BOUCK D, DUFFY S, *et al.* **Chemical genetics of Plasmodium falciparum**. Nature. 2010 May 20, vol. 465, n° 7296, pp.311-315
http://dx.doi.org/10.1038/nature09099 **(accès payant)**

Malaria caused by Plasmodium falciparum is a disease that is responsible for 880,000 deaths per year worldwide. Vaccine development has proved difficult and resistance has emerged for most antimalarial drugs. To discover new antimalarial chemotypes, we have used a phenotypic forward chemical genetic approach to assay 309,474 chemicals. Here we disclose structures and biological activity of the entire library-many of which showed potent in vitro activity against drug-resistant P. falciparum strains-and detailed profiling of 172 representative candidates. A reverse chemical genetic study identified 19 new inhibitors of 4 validated drug targets and 15 novel binders among 61 malarial proteins. Phylochemogenetic profiling in several organisms revealed similarities between Toxoplasma gondii and mammalian cell lines and dissimilarities between P. falciparum and related protozoans. One exemplar compound displayed efficacy in a murine model. Our findings provide the scientific community with new starting points for malaria drug discovery

(5) KHOR CC, VANNBERG FO, CHAPMAN SJ, GUO H, *et al.* **CISH and susceptibility to infectious diseases**. N Engl J Med. 2010 June 3, vol. 362, n° 22, pp.2092-2101
http://dx.doi.org/10.1056/NEJMoa0905606 **(accès réservé EHESP)**

BACKGROUND: The interleukin-2-mediated immune response is critical for host defense against infectious pathogens. Cytokine-inducible SRC homology 2 (SH2) domain protein (CISH), a suppressor of cytokine signaling, controls interleukin-2 signaling. METHODS: Using a case-control design, we tested for an association between CISH polymorphisms and susceptibility to major infectious diseases (bacteremia, tuberculosis, and severe malaria) in blood samples from 8402 persons in Gambia, Hong Kong, Kenya, Malawi, and Vietnam. We had previously tested 20 other immune-related genes in one or more of these sample collections. RESULTS: We observed associations between variant alleles of multiple CISH polymorphisms and increased susceptibility to each infectious disease in each of the study populations. When all five single-nucleotide polymorphisms (SNPs) (at positions -639, -292, -163, +1320, and +3415 [all relative to CISH]) within the CISH-associated locus were considered together in a multiple-SNP score, we found an association between CISH genetic variants and susceptibility to bacteremia, malaria, and tuberculosis (P=3.8x10(-11) for all comparisons), with -292 accounting for most of the association signal (P=4.58x10(-7)). Peripheral-blood mononuclear cells obtained from adult subjects carrying the -292 variant, as compared with wild-type cells, showed a muted response to the stimulation of interleukin-2 production--that is, 25 to 40% less CISH expression. CONCLUSIONS: Variants of CISH are associated with susceptibility to diseases caused by diverse infectious pathogens, suggesting that negative regulators of cytokine signaling have a role in immunity against various

infectious diseases. The overall risk of one of these infectious diseases was increased by at least 18% among persons carrying the variant CISH alleles

(6) LEDFORD H. **Malaria may not rise as world warms**. Nature. 2010 May 20, vol. 465, n° 7296, pp.280-281
http://dx.doi.org/10.1038/465280a **(accès payant)**

(7) NEWMAN RD. **Malaria control beyond 2010**. BMJ. 2010, vol. 340, p.c2714
http://www.ncbi.nlm.nih.gov/pubmed/20543011

(8) REYBURN H. **New WHO guidelines for the treatment of malaria**. BMJ. 2010, vol. 340, p.c2637
http://www.ncbi.nlm.nih.gov/pubmed/20511305

(9) TIMMANN C, MEYER CG. **King Tutankhamun's family and demise**. JAMA. 2010 June 23, vol. 303, n° 24, pp.2473-2475
http://dx.doi.org/10.1001/jama.2010.822 **(accès réservé EHESP)**

Pathologies liées à l'obésité

sommaire

(1) AL SS, GRAHAM JE, KUO YF, GOODWIN JS, *et al.* **Obesity and disability: relation among older adults living in Latin America and the Caribbean**. Am J Epidemiol. 2010 June 15, vol. 171, n° 12, pp.1282-1288
http://dx.doi.org/10.1093/aje/kwq087 **(accès réservé EHESP)**

The prevalence and incidence of both obesity and disability are projected to increase in the coming decades. The authors examined the relation between obesity and disability in older adults from 6 Latin American cities participating in the Health, Well-Being and Aging in Latin America and the Caribbean (SABE) Study (1999-2000). The sample included 6,166 participants aged 65 years or more. Data on sociodemographic factors, smoking status, medical conditions, body mass index (BMI; weight (kg)/height (m)(2)), and self-reported activities of daily living (ADL) were obtained. The prevalence of obesity (BMI > or = 30) ranged from 13.3% in Havana, Cuba, to 37.6% in Montevideo, Uruguay. Using a BMI of 18.5-<25 as the reference category and controlling for all covariates, the lowest odds ratio for ADL limitation was for a BMI of 25-<30 (odds ratio = 1.10, 95% confidence interval: 0.93, 1.30), and the highest odds ratio for ADL limitation was for a BMI of 35 or higher (odds ratio = 1.63, 95% confidence interval: 1.26, 2.11). The results indicated that obesity is an independent factor contributing to ADL disability in these populations and should be included in future planning to reduce the impact of disability on global health

(2) BAER HJ, TWOROGER SS, HANKINSON SE, WILLETT WC. **Body fatness at young ages and risk of breast cancer throughout life**. Am J Epidemiol. 2010 June 1, vol. 171, n° 11, pp.1183-1194
http://dx.doi.org/10.1093/aje/kwq045 **(accès réservé EHESP)**

Body fatness at young ages may be related to breast cancer risk independently of adult adiposity. The authors conducted a prospective analysis among 188,860 women (7,582 breast cancer cases) in the Nurses' Health Study (1988-2004) and Nurses' Health Study II (1989-2005) who recalled their body fatness at ages 5, 10, and 20 years using a 9-level pictogram (level 1: most lean; level 9: most overweight). Body fatness at young ages was inversely associated with risk of both premenopausal and postmenopausal breast cancer (per 1-unit increase in adolescent body fatness, relative risk (RR) = 0.88 and RR = 0.91, respectively; P(trend) < 0.0001). Among all

women, the RR for adolescent body fatness of level 6.5 or higher versus level 1 was 0.57 (per 1-unit increase, RR = 0.90; P(trend) < 0.0001) and was unaffected by adjustment for current body mass index. The association was stronger for women with birth weights under 8.5 pounds (<3.9 kg) than for women with birth weights of 8.5 pounds or more (> or =3.9 kg) (per 1-unit increase, RR = 0.89 and RR = 0.94, respectively; P(interaction) = 0.04) and stronger for estrogen receptor-negative tumors than for estrogen receptor-positive tumors (per 1-unit increase, RR = 0.86 and RR = 0.92, respectively; P(heterogeneity) = 0.03). Body fatness at young ages has a strong and independent inverse relation to breast cancer risk throughout life

(3) BAJOS N, WELLINGS K, LABORDE C, MOREAU C. **Sexuality and obesity, a gender perspective: results from French national random probability survey of sexual behaviours**. BMJ. 2010, vol. 340, p.c2573
http://www.ncbi.nlm.nih.gov/pubmed/20551118

OBJECTIVES: To analyse the association between body mass index (BMI) and sexual activity, sexual satisfaction, unintended pregnancies, and abortions in obese people and to discuss the implications for public health practices, taking into account the respondents' and their partners' BMI. DESIGN: Random probability survey of sexual behaviours. SETTING: National population based survey of 12 364 men and women aged 18-69 living in France in 2006. PARTICIPANTS: Random selection of 5535 women and 4635 men, of whom 3651 women and 2725 men were normal weight (BMI 18.5-<25), 1010 women and 1488 men were overweight (BMI 25-<30), and 411 women and 350 men were obese (BMI >30). RESULTS: Obese women were less likely than normal weight women to report having a sexual partner in the past 12 months (odds ratio 0.71, 95% confidence interval 0.51 to 0.97). Obese men were less likely than normal weight men to report more than one sexual partner in the same period (0.31, 0.17 to 0.57, P<0.001) and more likely to report erectile dysfunction (2.58, 1.09 to 6.11, P<0.05). Sexual dysfunction was not associated with BMI among women. Obese women aged under 30 were less likely to seek healthcare services for contraception (0.37, 0.18 to 0.76) or to use oral contraceptives (0.34, 0.15 to 0.78). They were also more likely to report an unintended pregnancy (4.26, 2.21 to 8.23). CONCLUSION: There is a link between BMI and sexual behaviour and adverse sexual health outcomes, with obese women less likely to access contraceptive healthcare services and having more unplanned pregnancies. Prevention of unintended pregnancies among these women is a major reproductive health challenge. Healthcare professionals need to be aware of sensitivities related to weight and gender in the provision of sexual health services

(4) BOWMAN J. **Perioperative mortality and long-term survival in live kidney donors**. JAMA. 2010 June 9, vol. 303, n° 22, pp.2249-2250
http://dx.doi.org/10.1001/jama.2010.729 **(accès réservé EHESP)**

(5) BROWN JE, BROOM DH, NICHOLSON JM, BITTMAN M. **Do working mothers raise couch potato kids? Maternal employment and children's lifestyle behaviours and weight in early childhood**. Soc Sci Med. 2010 June, vol. 70, n° 11, pp.1816-1824
http://dx.doi.org/10.1016/j.socscimed.2010.01.040 **(accès réservé EHESP)**

Alarm about the increasing prevalence of childhood obesity has focussed attention on individual lifestyle behaviours that may contribute to unhealthy weight. More distal predictors such as maternal employment may also be implicated since working mothers have less time to supervise children's daily activities. The research reported here used two waves of data from the Longitudinal Study of Australian Children to investigate whether mothers' hours in paid work shape young children's television viewing, snacking and physical activity, and through those lifestyle behaviours, children's weight at ages 4-5 years and 6-7 years. At both ages, children's lifestyle behaviours were interrelated and associated with weight status. Cross-sectional analysis confirmed small, direct associations between longer hours of maternal employment and child weight at age 4-5 years, but not with child's weight measured two years later. In both the cross-sectional and prospective analyses, the children of mothers who worked part-time watched less television and were less likely to be overweight than children of mothers who were not employed or who worked full-time. While associations were small, they remained significant after adjustment

for maternal weight, household income and other factors. The combination of direct and indirect relationships between mothers' work hours and the weight status of their young children provides additional support to calls for family-friendly work policies as an important means for promoting healthy family lifestyles and early childhood wellbeing

(6) CASERTA CA, PENDINO GM, AMANTE A, VACALEBRE C, *et al.* **Cardiovascular risk factors, nonalcoholic fatty liver disease, and carotid artery intima-media thickness in an adolescent population in southern Italy**. Am J Epidemiol. 2010 June 1, vol. 171, n° 11, pp.1195-1202
http://dx.doi.org/10.1093/aje/kwq073 **(accès réservé EHESP)**

The objective of this study was to determine, in an adolescent population, the prevalence of nonalcoholic fatty liver disease (NAFLD) and the association of NAFLD and cardiovascular risk factors with carotid artery intima-media thickness (IMT), a marker of subclinical atherosclerosis. The authors conducted a population-based study among 642 randomly selected adolescents aged 11-13 years in Reggio Calabria, southern Italy, between November 2007 and October 2008. Prevalences of overweight and obesity were 30.5% and 13.5%, respectively. The overall prevalence of NAFLD was 12.5%, increasing to 23.0% in overweight/obese adolescents. In univariate analysis, increased IMT was positively associated with the presence of NAFLD, body mass index (BMI), waist circumference, systolic blood pressure (all P's < 0.001), diastolic blood pressure (P = 0.006), gamma-glutamyl transpeptidase (P = 0.006), alanine aminotransferase (P = 0.007), and C-reactive protein (P = 0.008) and was inversely associated with high density lipoprotein cholesterol (P < 0.001). In multivariate analysis, NAFLD (P = 0.002), BMI (P = 0.004), waist circumference (P = 0.003), and systolic blood pressure (P = 0.005) retained significant associations. The authors conclude that NAFLD, BMI, waist circumference, and systolic blood pressure are independent markers of increased IMT in a random sample of adolescents

(7) GILL TP, BAUR LA, KING LA. **Should health policy focus on physical inactivity rather than obesity? No**. BMJ. 2010, vol. 340, p.c2602
http://www.ncbi.nlm.nih.gov/pubmed/20501585

(8) GOLDBECK-WOOD S. **Obesity and poor sexual health outcomes**. BMJ. 2010, vol. 340, p.c2826
http://www.ncbi.nlm.nih.gov/pubmed/20551119

(9) ISHIBASHI J, SEALE P. **Medicine. Beige can be slimming**. Science. 2010 May 28, vol. 328, n° 5982, pp.1113-1114
http://dx.doi.org/10.1126/science.1190816 **(accès réservé EHESP)**

(10) KAHN HS. **Physical activity and preventing weight gain in women**. JAMA. 2010 June 23, vol. 303, n° 24, p.2475
http://dx.doi.org/10.1001/jama.2010.824 **(accès réservé EHESP)**

(11) KWATRA SG. **Physical activity and preventing weight gain in women**. JAMA. 2010 June 23, vol. 303, n° 24, pp.2475-2476
http://dx.doi.org/10.1001/jama.2010.825 **(accès réservé EHESP)**

(12) NESTLE M. **Health care reform in action--calorie labeling goes national**. N Engl J Med. 2010 June 24, vol. 362, n° 25, pp.2343-2345
http://dx.doi.org/10.1056/NEJMp1003814 **(accès réservé EHESP)**

(13) O'BRIEN PE. **Failure to report financial disclosure information in a study of gastric banding in adolescent obesity**. JAMA. 2010 June 16, vol. 303, n° 23, p.2357

http://dx.doi.org/10.1001/jama.2010.693 **(accès réservé EHESP)**

(14) ORTEGA FB, ARTERO EG. **Re: "Cardiorespiratory fitness levels among us adults 20-49 years of age: findings from the 1999-2004 National Health and Nutrition Examination Survey"**. Am J Epidemiol. 2010 June 15, vol. 171, n° 12, pp.1323-1324
http://dx.doi.org/10.1093/aje/kwq145 **(accès réservé EHESP)**

(15) PINOT DE MA, POWER C, LI L. **Changing influences on childhood obesity: a study of 2 generations of the 1958 British birth cohort**. Am J Epidemiol. 2010 June 15, vol. 171, n° 12, pp.1289-1298
http://dx.doi.org/10.1093/aje/kwq083 **(accès réservé EHESP)**

Explanations for the trend of increasing childhood obesity have yet to be identified. The authors examined members of the 1958 British birth cohort (age 7 years, n = 8,552) and offspring (ages 4-9 years, n = 1,889) born to mothers under age 30 years to establish whether risk factors for childhood obesity have changed over time (1965-1991). The authors applied multilevel linear and logistic models that account for within-family correlations in order to examine associations between risk factors and childhood body mass index (BMI; weight (kg)/height (m)(2)) (age- and sex-specific standard deviation scores and overweight/obesity) in the 2 populations. The authors found that the prevalence of overweight/obesity had increased by more than 50% between generations. Parental BMI and full-time maternal employment were both positively associated with offspring BMI in childhood (e.g., an increase of 0.4-0.5 units for maternal employment); these associations had strengthened between generations. There was evidence of a widening social gap in childhood obesity: Indicators of lower socioeconomic position showed either no association or a protective effect in cohort members but were associated with increased BMI in offspring. Prevalences of parental obesity and maternal employment had increased. Socioeconomic factors had improved across generations. Parental obesity, maternal employment, and socioeconomic factors may play an increasing role in the childhood obesity epidemic

(16) RICHARDSON LA. **Laparoscopic gastric banding vs lifestyle intervention in severely obese adolescents**. JAMA. 2010 June 16, vol. 303, n° 23, pp.2356-2357
http://dx.doi.org/10.1001/jama.2010.781 **(accès réservé EHESP)**

(17) SUTTON-TYRRELL K, ZHAO X, SANTORO N, LASLEY B, *et al.* **Reproductive hormones and obesity: 9 years of observation from the Study of Women's Health Across the Nation**. Am J Epidemiol. 2010 June 1, vol. 171, n° 11, pp.1203-1213
http://dx.doi.org/10.1093/aje/kwq049 **(accès réservé EHESP)**

The effect of change in reproductive hormones and menopause on incident obesity (body mass index > or =30 kg/m(2)) and severe obesity (body mass index > or =35 kg/m(2)) was evaluated over 9 years in 3,260 US women recruited in the multiethnic Study of Women's Health Across the Nation in 1996-1997. After 9 years, cumulative incidences of obesity and severe obesity reached 21.8% and 12.3%, respectively. In multivariate analysis, hormone changes, chronic health conditions, lower physical activity, race/ethnicity, and age were significantly associated with incident obesity and/or severe obesity. The odds of incident severe obesity increased with surgical menopause (odds ratio (OR) = 5.07, 95% confidence interval (CI): 2.29, 11.20; P < 0.001) and initiation of hormone therapy prior to 12 months of amenorrhea (OR = 2.94, 95% CI: 1.14, 7.58; P = 0.03). Predictors of obesity included an increase in free androgen index (OR = 1.37, 95% CI: 1.12, 1.68; P = 0.002) and a decrease in sex hormone-binding globulin (OR = 0.60, 95% CI: 0.45, 0.80; P = 0.0005). Similar results were found for severe obesity. Obesity rates varied by race, but no hormone-by-race interactions were observed. These longitudinal data demonstrate that higher androgens, lower sex hormone-binding globulin, surgical menopause, and early hormone therapy use predict incident obesity and/or severe obesity in a multiracial cohort of women transitioning into menopause

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http://dx.doi.org/10.1126/science.1186034 **(accès réservé EHESP)**

Obesity results from chronic energy surplus and excess lipid storage in white adipose tissue (WAT). In contrast, brown adipose tissue (BAT) efficiently burns lipids through adaptive thermogenesis. Studying mouse models, we show that cyclooxygenase (COX)-2, a rate-limiting enzyme in prostaglandin (PG) synthesis, is a downstream effector of beta-adrenergic signaling in WAT and is required for the induction of BAT in WAT depots. PG shifted the differentiation of defined mesenchymal progenitors toward a brown adipocyte phenotype. Overexpression of COX-2 in WAT induced de novo BAT recruitment in WAT, increased systemic energy expenditure, and protected mice against high-fat diet-induced obesity. Thus, COX-2 appears integral to de novo BAT recruitment, which suggests that the PG pathway regulates systemic energy homeostasis

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SIDA

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http://dx.doi.org/10.1056/NEJMoa0911486 **(accès réservé EHESP)**

BACKGROUND: We evaluated the efficacy of a maternal triple-drug antiretroviral regimen or infant nevirapine prophylaxis for 28 weeks during breast-feeding to reduce postnatal transmission of human immunodeficiency virus type 1 (HIV-1) in Malawi. METHODS: We randomly assigned 2369 HIV-1-positive, breast-feeding mothers with a CD4+ lymphocyte count of at least 250 cells per cubic millimeter and their infants to receive a maternal antiretroviral regimen, infant nevirapine, or no extended postnatal antiretroviral regimen (control group). All mothers and infants received perinatal prophylaxis with single-dose nevirapine and 1 week of zidovudine plus lamivudine. We used the Kaplan-Meier method to estimate the cumulative risk of HIV-1 transmission or death by 28 weeks among infants who were HIV-1-negative 2 weeks after birth. Rates were compared with the use of the log-rank test. RESULTS: Among mother-infant pairs, 5.0% of infants were HIV-1-positive at 2 weeks of life. The estimated risk of HIV-1 transmission between 2 and 28 weeks was higher in the control group (5.7%) than in either the maternal-regimen group (2.9%, P=0.009) or the infant-regimen group (1.7%, P<0.001). The estimated risk of infant HIV-1 infection or death between 2 and 28 weeks was 7.0% in the control group, 4.1% in the maternal-regimen group (P=0.02), and 2.6% in the infant-regimen group (P<0.001). The proportion of women with neutropenia was higher among those receiving the antiretroviral regimen (6.2%) than among those in either the nevirapine group (2.6%) or the control group (2.3%). Among infants receiving nevirapine, 1.9% had a hypersensitivity reaction. CONCLUSIONS: The use of either a maternal antiretroviral regimen or infant nevirapine for 28 weeks was effective in reducing HIV-1 transmission during breast-feeding. (ClinicalTrials.gov number, NCT00164736.)

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http://dx.doi.org/10.1016/S0140-6736(10)60705-2 **(accès réservé EHESP)**

BACKGROUND: High plasma HIV-1 RNA concentrations are associated with increased risk of HIV-1 transmission. Initiation of antiretroviral therapy (ART) reduces plasma HIV-1 concentrations. We aimed to assess the effect of ART use by patients infected with HIV-1 on risk of transmission to their uninfected partners. METHODS: Participants in our prospective cohort analysis were from a randomised placebo-controlled trial that enrolled heterosexual African adults who were seropositive for both HIV-1 and herpes simplex virus type 2, and their HIV-1 seronegative partners. At enrolment, HIV-1 infected participants had CD4 counts of 250 cells per microL or greater and did not meet national guidelines for ART initiation; during 24 months of follow-up, CD4 counts were measured every 6 months and ART was initiated in accordance with national guidelines. Uninfected partners were tested for HIV-1 every 3 months. The primary outcome was genetically-linked HIV-1 transmission within the study partnership. We assessed rates of HIV-1 transmission by ART status of infected participants. FINDINGS: 3381 couples were eligible for analysis. 349 (10%) participants with HIV-1 initiated ART during the study, at a median CD4 cell count of 198 (IQR 161-265) cells per microL. Only one of 103 genetically-linked HIV-1 transmissions was from an infected participant who had started ART, corresponding to transmission rates of 0.37 (95% CI 0.09-2.04) per 100 person-years in those who had initiated treatment and 2.24 (1.84-2.72) per 100 person-years in those who had not-a 92% reduction (adjusted incidence rate ratio 0.08, 95% CI 0.00-0.57, p=0.004). In participants not on ART, the highest HIV-1 transmission rate (8.79 per 100 person-years) was from those with CD4 cell counts lower than 200 cells per microL. In couples in whom the untreated HIV-1 infected partner had a CD4 cell count greater than 200 cells per microL, 66 (70%) of 94 transmissions occurred when plasma HIV-1 concentrations exceeded 50 000 copies per mL. INTERPRETATION: Low CD4 cell counts and high plasma HIV-1 concentrations might guide use of ART to achieve an HIV-1 prevention benefit. Provision of ART to HIV-1 infected patients could be an effective strategy to achieve population-level reductions in HIV-1 transmission. FUNDING: Bill & Melinda Gates Foundation; US National Institutes of Health

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http://dx.doi.org/10.1038/nature08997 **(accès payant)**

Without therapy, most people infected with human immunodeficiency virus (HIV) ultimately progress to AIDS. Rare individuals ('elite controllers') maintain very low levels of HIV RNA without therapy, thereby making disease progression and transmission unlikely. Certain HLA class I alleles are markedly enriched in elite controllers, with the highest association observed for HLA-B57 (ref. 1). Because HLA molecules present viral peptides that activate CD8(+) T cells, an immune-mediated mechanism is probably responsible for superior control of HIV. Here we describe how the peptide-binding characteristics of HLA-B57 molecules affect thymic development such that, compared to other HLA-restricted T cells, a larger fraction of the naive repertoire of B57-restricted clones recognizes a viral epitope, and these T cells are more cross-reactive to mutants of targeted epitopes. Our calculations predict that such a T-cell repertoire imposes strong immune pressure on immunodominant HIV epitopes and emergent mutants, thereby promoting efficient control of the virus. Supporting these predictions, in a large cohort of HLA-typed individuals, our experiments show that the relative ability of HLA-B alleles to control HIV correlates with their peptide-binding characteristics that affect thymic development. Our results provide a conceptual framework that unifies diverse empirical observations, and have implications for vaccination strategies

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http://dx.doi.org/10.1016/j.socscimed.2010.01.018 **(accès réservé EHESP)**

The 2008 food crisis may have increased household food insecurity and caused distress among impoverished populations in low-income countries. Policy researchers have attempted to quantify the impact that a sharp rise in food prices might have on population wellbeing by asking what proportion of households would drop below conventional poverty lines given a set increase in prices. Our understanding of the impact of food crises can be extended by conducting micro-level ethnographic studies. This study examined self-reported household food insecurity (FI) and common mental disorders (CMD) among 110 community health AIDS care volunteers living in Addis Ababa, Ethiopia during the height of the 2008 food crisis. We used generalized estimating equations that account for associations between responses given by the same participants over 3 survey rounds during 2008, to model the longitudinal response profiles of FI, CMD symptoms, and socio-behavioral and micro-economic covariates. To help explain the patterns observed in the response profiles and regression results, we examine qualitative data that contextualize the cognition and reporting behavior of AIDS care volunteers, as well as potential observation biases inherent in longitudinal, community-based research. Our data show that food insecurity is highly prevalent, that is it associated with household economic factors, and that it is linked to mental health. Surprisingly, the volunteers in this urban sample did not report increasingly severe FI or CMD during the peak of the 2008 food crisis. This is a counter-intuitive result that would not be predicted in analyses of population-level data such as those used in econometrics simulations. But when these results are linked to real people in specific urban ecologies, they can improve our understanding of the psychosocial consequences of food price shocks

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http://dx.doi.org/10.1056/NEJMoa0907736 **(accès réservé EHESP)**

BACKGROUND: The most effective highly active antiretroviral therapy (HAART) to prevent mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1) in pregnancy and its efficacy during breast-feeding are unknown. METHODS: We randomly assigned 560 HIV-1-infected pregnant women (CD4+ count, > or = 200 cells per cubic millimeter) to receive coformulated abacavir, zidovudine, and lamivudine (the nucleoside reverse-transcriptase inhibitor [NRTI] group) or lopinavir-ritonavir plus zidovudine-lamivudine (the protease-inhibitor group) from 26 to 34 weeks' gestation through planned weaning by 6 months post partum. A total of 170 women with CD4+ counts of less than 200 cells per cubic millimeter received nevirapine plus zidovudine-lamivudine (the observational group). Infants received single-dose nevirapine and 4 weeks of zidovudine. RESULTS: The rate of virologic suppression to less than 400 copies per milliliter was high and did not differ significantly among the three groups at delivery (96% in the NRTI group, 93% in the protease-inhibitor group, and 94% in the observational group) or

throughout the breast-feeding period (92% in the NRTI group, 93% in the protease-inhibitor group, and 95% in the observational group). By 6 months of age, 8 of 709 live-born infants (1.1%) were infected (95% confidence interval [CI], 0.5 to 2.2): 6 were infected in utero (4 in the NRTI group, 1 in the protease-inhibitor group, and 1 in the observational group), and 2 were infected during the breast-feeding period (in the NRTI group). Treatment-limiting adverse events occurred in 2% of women in the NRTI group, 2% of women in the protease-inhibitor group, and 11% of women in the observational group. CONCLUSIONS: All regimens of HAART from pregnancy through 6 months post partum resulted in high rates of virologic suppression, with an overall rate of mother-to-child transmission of 1.1%. (ClinicalTrials.gov number, NCT00270296.)

Tuberculose

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http://dx.doi.org/10.1016/S0140-6736(10)60492-8 **(accès réservé EHESP)**

BACKGROUND: Data from Kwazulu Natal, South Africa, suggest that almost all patients with extensively drug-resistant (XDR) tuberculosis are HIV-positive, with a fatal outcome. Since, there are few data for the treatment-related outcomes of XDR tuberculosis in settings with a high HIV prevalence, we investigated the associations of these diseases in such settings to formulate recommendations for control programmes. METHODS: In a retrospective cohort study, we analysed the case records of patients (>16 years old) with XDR tuberculosis (culture-proven at diagnosis) between August, 2002, and February, 2008, at four designated provincial treatment facilities in South Africa. We used Cox proportional hazards regression models to assess risk factors associated with the outcomes-mortality and culture conversion. FINDINGS: 195 of 227 patients were analysed. 21 died before initiation of any treatment, and 174 patients (82 with HIV infection) were treated. 62 (36%) of these patients died during follow-up. The number of deaths was not significantly different in patients with or without HIV infection: 34 (41%) of 82 versus 28 (30%) of 92 (p=0.13). Treatment with moxifloxacin (hazard ratio 0.11, 95% CI 0.01-0.82; p=0.03), previous culture-proven multidrug-resistant tuberculosis (5.21, 1.93-14.1; p=0.001), and number of drugs used in a regimen (0.59, 0.45-0.78, p<0.0001) were independent predictors of death. Fewer deaths occurred in patients with HIV infection given highly active antiretroviral therapy than in those who were not (0.38, 0.18-0.80; p=0.01). 33 (19%) of 174 patients showed culture conversion, of which 23 (70%) converted within 6 months of initiation of treatment. INTERPRETATION: In South Africa, patients with XDR tuberculosis, a substantial proportion of whom are not infected with HIV, have poor management outcomes. Nevertheless, survival in patients with HIV infection is better than previously reported. The priorities for the country are still prevention of XDR tuberculosis, and early detection and management of multidrug-resistant and XDR tuberculosis through strengthened programmes and laboratory capacity. FUNDING: South

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http://dx.doi.org/10.1016/S0140-6736(10)60410-2 **(accès réservé EHESP)**

Although progress has been made to reduce global incidence of drug-susceptible tuberculosis, the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis during the past decade threatens to undermine these advances. However, countries are responding far too slowly. Of the estimated 440,000 cases of MDR tuberculosis that occurred in 2008, only 7% were identified and reported to WHO. Of these cases, only a fifth were treated according to WHO standards. Although treatment of MDR and XDR tuberculosis is possible with currently available diagnostic techniques and drugs, the treatment course is substantially more costly and laborious than for drug-susceptible tuberculosis, with higher rates of treatment failure and mortality. Nonetheless, a few countries provide examples of how existing technologies can be used to reverse the epidemic of MDR tuberculosis within a decade. Major improvements in laboratory capacity, infection control, performance of tuberculosis control programmes, and treatment regimens for both drug-susceptible and drug-resistant disease will be needed, together with a massive scale-up in diagnosis and treatment of MDR and XDR tuberculosis to prevent drug-resistant strains from becoming the dominant form of tuberculosis. New diagnostic tests and drugs are likely to become available during the next few years and should accelerate control of MDR and XDR tuberculosis. Equally important, especially in the highest-burden countries of India, China, and Russia, will be a commitment to tuberculosis control including improvements in national policies and health systems that remove financial barriers to treatment, encourage rational drug use, and create the infrastructure necessary to manage MDR tuberculosis on a national scale

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http://dx.doi.org/10.1016/S0140-6736(10)60409-6 **(accès réservé EHESP)**

Despite policies, strategies, and guidelines, the epidemic of HIV-associated tuberculosis continues to rage, particularly in southern Africa. We focus our attention on the regions with the greatest burden of disease, especially sub-Saharan Africa, and concentrate on prevention of tuberculosis in people with HIV infection, a challenge that has been greatly neglected. We argue

for a much more aggressive approach to early diagnosis and treatment of HIV infection in affected communities, and propose urgent assessment of frequent testing for HIV and early start of antiretroviral treatment (ART). This approach should result in short-term and long-term declines in tuberculosis incidence through individual immune reconstitution and reduced HIV transmission. Implementation of the 3Is policy (intensified tuberculosis case finding, infection control, and isoniazid preventive therapy) for prevention of HIV-associated tuberculosis, combined with earlier start of ART, will reduce the burden of tuberculosis in people with HIV infection and provide a safe clinical environment for delivery of ART. Some progress is being made in provision of HIV care to HIV-infected patients with tuberculosis, but too few receive co-trimoxazole prophylaxis and ART. We make practical recommendations about how to improve this situation. Early HIV diagnosis and treatment, the 3Is, and a comprehensive package of HIV care, in association with directly observed therapy, short-course (DOTS) for tuberculosis, form the basis of prevention and control of HIV-associated tuberculosis. This call to action recommends that both HIV and tuberculosis programmes exhort implementation of strategies that are known to be effective, and test innovative strategies that could work. The continuing HIV-associated tuberculosis epidemic needs bold but responsible action, without which the future will simply mirror the past

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(12) KAUFMANN SH, HUSSEY G, LAMBERT PH. **New vaccines for tuberculosis**. Lancet. 2010 June 12, vol. 375, n° 9731, pp.2110-2119
http://dx.doi.org/10.1016/S0140-6736(10)60393-5 **(accès réservé EHESP)**

New vaccines are urgently needed if we want to reach the goal of substantially reducing the incidence of tuberculosis by 2050. Despite a steady increase in funding over the past decade, there is still a striking financial shortfall for vaccine research and development for tuberculosis. Yet, around ten vaccine candidates have left the laboratory stage and entered clinical trials. These vaccines are either aimed at replacing the present vaccine, BCG, or at enhancing immunity induced by BCG. However, these pre-exposure candidates are designed for prevention of disease and will therefore neither eradicate the pathogen, nor prevent stable infection. Long-term vaccination strategies need to target these more ambitious goals. Even though vaccine development will have a price, the return of investment will greatly exceed original costs

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BACKGROUND: The interleukin-2-mediated immune response is critical for host defense against infectious pathogens. Cytokine-inducible SRC homology 2 (SH2) domain protein (CISH), a suppressor of cytokine signaling, controls interleukin-2 signaling. METHODS: Using a case-control design, we tested for an association between CISH polymorphisms and susceptibility to major infectious diseases (bacteremia, tuberculosis, and severe malaria) in blood samples from 8402 persons in Gambia, Hong Kong, Kenya, Malawi, and Vietnam. We had previously tested 20 other immune-related genes in one or more of these sample collections. RESULTS: We observed associations between variant alleles of multiple CISH polymorphisms and increased susceptibility to each infectious disease in each of the study populations. When all five single-nucleotide polymorphisms (SNPs) (at positions -639, -292, -163, +1320, and +3415 [all relative to CISH]) within the CISH-associated locus were considered together in a multiple-SNP score, we found an association between CISH genetic variants and susceptibility to bacteremia, malaria, and tuberculosis (P=3.8x10(-11) for all comparisons), with -292 accounting for most of the association signal (P=4.58x10(-7)). Peripheral-blood mononuclear cells obtained from adult subjects carrying the -292 variant, as compared with wild-type cells, showed a muted response to the stimulation of interleukin-2 production--that is, 25 to 40% less CISH expression. CONCLUSIONS: Variants of CISH are associated with susceptibility to diseases caused by diverse infectious pathogens, suggesting that negative regulators of cytokine signaling have a role in immunity against various

infectious diseases. The overall risk of one of these infectious diseases was increased by at least 18% among persons carrying the variant CISH alleles

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http://dx.doi.org/10.1016/S0140-6736(10)60483-7 **(accès réservé EHESP)**

Rapid expansion of the standardised approach to tuberculosis diagnosis and treatment that is recommended by WHO allowed more than 36 million people to be cured between 1995 and 2008, averting up to 6 million deaths. Yet tuberculosis remains a severe global public health threat. There are more than 9 million new cases every year worldwide, and the incidence rate is falling at less than 1% per year. Although the overall target related to the Millennium Development Goals of halting and beginning to reverse the epidemic might have already been reached in 2004, the more important long-term elimination target set for 2050 will not be met with present strategies and instruments. Several key challenges persist. Many vulnerable people do not have access to affordable services of sufficient quality. Technologies for diagnosis, treatment, and prevention are old and inadequate. Multidrug-resistant tuberculosis is a serious threat in many settings. HIV/AIDS continues to fuel the tuberculosis epidemic, especially in Africa. Furthermore, other risk factors and underlying social determinants help to maintain tuberculosis in the community. Acceleration of the decline towards elimination of this disease will need invigorated actions in four broad areas: continued scale-up of early diagnosis and proper treatment for all forms of tuberculosis in line with the Stop TB Strategy; development and enforcement of bold health-system policies; establishment of links with the broader development agenda; and promotion and intensification of research towards innovations

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Drugs for tuberculosis are inadequate to address the many inherent and emerging challenges of treatment. In the past decade, ten compounds have progressed into the clinical development pipeline, including six new compounds specifically developed for tuberculosis. Despite this progress, the global drug pipeline for tuberculosis is still insufficient to address the unmet needs of treatment. Additional and sustainable efforts, and funding are needed to further improve the pipeline. The key challenges in the development of new treatments are the needs for novel drug combinations, new trial designs, studies in paediatric populations, increased clinical trial capacity, clear regulatory guidelines, and biomarkers for prediction of long-term outcome. Despite substantial progress in efforts to control tuberculosis, the global burden of this disease remains high. To eliminate tuberculosis as a public health concern by 2050, all responsible parties need to work together to strengthen the global antituberculosis drug pipeline and support the development of new antituberculosis drug regimens

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BACKGROUND: Many DOTS experiences in developing countries have been reported. However, experience in a rural hospital and information on the differences between children and adults are limited. We described the epidemiology and treatment outcome of adult and childhood tuberculosis (TB) cases, and identified risk factors associated with defaulting and dying during TB treatment in a rural hospital over a 10-year period (1998 to 2007). METHODS: Retrospective data collection using TB registers and treatment cards in a rural private mission hospital. Information was collected on number of cases, type of TB and treatment outcomes using standardised definitions. RESULTS: 2225 patients were registered, 46.3% of whom were children. A total of 646 patients had smear-positive pulmonary TB (PTB), [132 (20.4%) children]; 816 had smear-negative PTB [556 (68.2%) children], and 763 extra-PTB (EPTB) [341 (44.8%) children]. The percentage of treatment defaulters was higher in paediatric (13.9%) than in adult patients (9.3%) (p = 0.001). The default rate declined from 16.8% to 3.5%, and was independently positively associated with TB meningitis (AOR: 2.8; 95% CI: 1.2-6.6) and negatively associated with smear-positive PTB (AOR: 0.6; 95% CI: 0.4-0.8). The mortality rate was 5.3% and the greatest mortality was associated with adult TB (AOR: 1.7; 95% CI: 1.1-2.5), TB meningitis (AOR: 3.6; 95% CI:1.2-10.9), and HIV infection (AOR: 4.3; 95% CI: 1.9-9.4). Decreased mortality was associated with TB lymphadenitis (AOR: 0.24; 95% CI: 0.11-0.57). CONCLUSION: (1) The registration of TB cases can be useful to understand the epidemiology of TB in local health facilities. (2) The defaulter and mortality rate of childhood TB is different to that of adult TB. (3) The rate of defaulting from treatment has declined over time

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