

Cuban Research in Current International Journals

The following selection—alphabetical by title—reflects Cuban medical publishing in international journals over the last quarter on an array of topics. Links to these journal articles may be found at www.medicc.org/mediccreview.

A qualitative glimpse at pharmaceutical care practice. Varela Dupotey NM, Ramalho de Oliveira D. *Pharm World Sci.* 2009 Dec;31(6):609–11.

This manuscript presents an argument for a broader use of qualitative methodologies to investigate the practice and the surroundings of pharmaceutical care. Albeit the use of qualitative research methods is growing in the health care field, it is still insufficient in the area of pharmaceutical care. Pharmaceutical care, as a patient-centered practice, calls for a more comprehensive and humanistic approach to research. It is our contention that the attempt to understand pharmaceutical care practice from the perspective of patients, pharmacists and other health care professionals, by means of using qualitative methods, would notably contribute to a better assessment of the value of pharmaceutical care programs in the health care system. Moreover, because a deeper understanding of the nuances of this practice can be achieved with the use of qualitative methods, this approach might also assist us in making the necessary changes to create more effective pharmaceutical care practices.

Assessment of vaccine potential of the *Neisseria*-specific protein NMB 0938. Sardiñas G, Climent Y, Rodríguez Y, González S, García D, Cobas K, et al. *Vaccine.* 2009 Nov 16;27(49):6910–17.

The availability of complete genome sequence of *Neisseria meningitidis* serogroup B strain MC58 and reverse vaccinology has allowed the discovery of several novel antigens. Here, we have explored the potential of *N. meningitidis* lipoprotein NMB0938 as a vaccine candidate, based on investigation of gene sequence conservation and the antibody response elicited after immunization in mice. This antigen was previously identified by a genome-based approach as an outer membrane lipoprotein unique to the *Neisseria* genus. The *nmb0938* gene was present in all 37 *Neisseria* isolates analyzed in this study. Based on amino acid sequence identity, 16 unique sequences were identified which clustered into three variants with identities ranging from 92 to 99%, with one cluster represented by the *Neisseria lactamica* strains. Recombinant protein NMB0938 (rNMB0938) was expressed in *Escherichia coli* and purified after solubilization of the insoluble fraction. Antisera produced in mice against purified rNMB0938 reacted with a range of meningococcal strains in whole-cell ELISA and western blotting.

Using flow cytometry, it was also shown that anti-rNMB0938 antibodies bound to the surface of the homologous meningococcal strain and activated complement deposition. Moreover, antibodies against rNMB0938 elicited complement-mediated killing of meningococcal strains from both sequence variants and conferred passive protection against meningococcal bacteremia in infant rats. According to our results, NMB0938 represents a promising candidate to be included in a vaccine to prevent meningococcal disease.

Identification of new meningococcal serogroup B surface antigens through a systematic analysis of neisserial genomes. Pajon R, Yero D, Niebla O, Climent Y, Sardiñas G, García D. *Vaccine.* 2009 Dec 11;28(2):532–41.

The difficulty of inducing an effective immune response against the *Neisseria meningitidis* serogroup B capsular polysaccharide has led to the search for vaccines for this serogroup based on outer membrane proteins. The availability of the first meningococcal genome (MC58 strain) allowed the expansion of high-throughput methods to explore the protein profile displayed by *N. meningitidis*. By combining a pan-genome analysis with an extensive experimental validation to identify new potential vaccine candidates, genes coding for antigens likely to be exposed on the surface of the meningococcus were selected after a multistep comparative analysis of entire *Neisseria* genomes. Eleven novel putative ORF annotations were reported for serogroup B strain MC58. Furthermore, a total of 20 new predicted potential pan-neisserial vaccine candidates were produced as recombinant proteins and evaluated using immunological assays. Potential vaccine candidate coding genes were PCR-amplified from a panel of representative strains and their variability analyzed using maximum likelihood approaches for detecting positive selection. Finally, five proteins all capable of inducing a functional antibody response vs *N. meningitidis* strain CU385 were identified as new attractive vaccine candidates: NMB0606 a potential YajC orthologue, NMB0928 the neisserial NlpB (BamC), NMB0873 a LolB orthologue, NMB1163 a protein belonging to a curli-like assembly machinery, and NMB0938 (a neisserial specific antigen) with evidence of positive selection appreciated for NMB0928. The new set of vaccine candidates and the novel proposed functions will open a new wave of research in the search for the elusive neisserial vaccine.

Laboratory-Based Surveillance of *Streptococcus pneumoniae* Invasive Disease in Children in 10 Latin American Countries: A SIREVA II Project, 2000–2005. Castañeda E, Agudelo CI, Reguerira M, Corso A, de Cunto Brandileone MC, Brandão AP, et al. *Pediatr Infect Dis J.* 2009 Sep;28(9):e265–e270.

Background For the last 14 years the Pan American Health Organization has been promoting surveillance of invasive pneumococcal disease in Latin American children for better understanding of the disease tendencies regarding capsular types circulation in each country and susceptibility to antimicrobials. **Methods** Laboratory-based surveillance data from 10 Latin American countries collected from 2000 to 2005 were analyzed, including serotype distribution and susceptibility to beta-lactam antibiotics. **Results** Although 61 different capsular types were identified during the 6-year surveillance, 13 serotypes accounted for 86% of all isolates. These were consistently the most prevalent throughout the study period with serotype 14 predominating. Diminished susceptibility to penicillin was detected in 38% of all *Streptococcus pneumoniae* isolates, with the highest prevalence in Dominican Republic and Mexico. Decreased susceptibility to penicillin increased in Brazil and Colombia whereas decreased high resistance rates was recorded in Chile. **Conclusions** These data indicate that 10 countries of the Region continue to have high quality laboratory-based surveillance for pneumococcal disease thus generating valuable information so that healthcare decision makers may prioritize interventions. The heptavalent vaccine will potentially cover from 52.4% to 76.5% of strains causing invasive pneumococcal disease and the 13 valent from 76.7% to 88.3%.

Morbimortality in heart and lung transplantation in Cuba: A 20-year follow-up. Bazán Milán M, Delgado Bereijo L, González Jiménez N. *Transplant Proc.* 2009 Oct;41(8):3507–9.

The first orthotopic heart transplantation (OHT) was performed in 1967 by C.N. Barnard in Cape Town, South Africa. The first OHT in Cuba was performed in 1985. The main purpose of our study was to determine some of the aspects related to the short-, mid-, and long-term morbimortality rates of OHT patients in Cuba. We analyzed the first 120 OHTs (3 heart plus lung transplantations, 4 retransplantations, and 113 heart transplantations) which were performed in Cuba from December 1985 to December

2005. Based on the analysis, we performed a descriptive, retrospective research about morbimortality. There was a predominance of the masculine sex (5.31:1). The overall mean age was 45.13 ± 11.58 years (range, 14–67 years). The most frequent pretransplant diagnosis was coronary artery disease (CAD; $n = 69$; 57.5%). Analyzing the Kaplan-Meier survival curve, we observed that the survival probability at 1 year was 83.3%; at 5 years, 45.7%; and at 10 years 19.2%. The complications by frequency were: sepsis ($n = 41$; 37%), acute rejection episodes ($n = 42$; 35.0%), and neoplasia ($n = 4$; 3.3%). Complications in frequency order were sepsis and acute rejection episodes among short term and chronic rejection and chronic renal failure among long-term survivors.

Randomized, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of live oral cholera vaccine 638 in Cuban adults. Valera R, García HM, Díaz Jidy M, Mirabal M, Armesto MI, Fando R, et al. *Vaccine*. 2009 Nov 5;27(47):6564–9.

A randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the safety, reactogenicity and the immunogenicity of a 2×10^9 CFU dose of the 638 lyophilized live attenuated cholera vaccine for oral administration, formulated and produced at Finlay Institute, City of Havana, Cuba. Thirty-six healthy female and male adult volunteers from 18 to 40 years old were involved, clinically examined and laboratory tested after the informed consent signature. Adverse events were monitored and seroconversion rates and geometrical mean titer (GMT) of vibriocidal antibodies were tested in volunteer's sera samples. Neither serious adverse events nor other damages to the volunteers due to vaccine or placebo feeding were reported during the clinical follow-up period of this study; none of the adverse events registered within the first 72h after inoculation were life-threatening for volunteers. Neither severe nor moderate adverse events were reported. Sixty-one percent of subjects showed mild expected adverse events in an interval lower than 24h up to the first 72h, 75% of these in the vaccinated group and 18% in the placebo group. Fourteen days after inoculation the GMT of vibriocidal antibodies in the vaccine group significantly increased in comparison to the placebo group. All subjects in the vaccine group (24) seroconverted (100%). Results show that this vaccine is safe, well tolerated and immunogenic in healthy female and male volunteers.

Recombinant nucleocapsid-like particles from dengue-2 virus induce protective CD4⁺ and CD8⁺ cells against viral encephalitis in mice. Gil L, López C, Lazo L, Valdés I, Marcos E, Alonso R, et al. *Int Immunol*. 2009 Oct;21(10):1175–83.

Virus-like particles are a highly effective type of subunit vaccine that mimics the overall

structure of virus particles without containing infectious genetic material. In this work, a particulate form of the recombinant capsid protein from dengue-2 was evaluated in mice to determine the level of protection against viral challenge and to measure the antigen-induced cell-mediated immunity (CMI). The nucleocapsid-like particles (NLPs) adjuvanted with alum did not induce antiviral antibodies. However, splenocytes from the immunized animals secreted high levels of IFN- γ upon virus stimulation, and a significant protection rate was achieved after challenge with lethal dengue-2 virus. Finally, both IFN- γ secretion and protection against viral encephalitis were demonstrated to be dependent on CD4⁺ and CD8⁺ cells. This study provides new evidences regarding the protective role of the CMI in the mouse model without the induction of neutralizing antibodies. Further studies in non-human primates or humanized mice should be carried out to elucidate the usefulness of the NLPs as a potential vaccine candidate against dengue disease.

Relapsing neuromyelitis optica: long term history and clinical predictors of death. Cabre P, González-Quevedo A, Bonnan M, Saiz A, Olindo S, Graus F, et al. *J Neurol Neurosurg Psychiatry*. 2009 Oct;80(10):1162–4.

Background Relapsing neuromyelitis optica (RNMO) is an uncommon but devastating inflammatory disorder of the central nervous system. Long term history in a wide series of RNMO is required for better knowledge of the course of the disease and identification of patients at high risk of death. **Methods** Clinical features of patients with RNMO (88 women/eight men) obtained from the geographic Caribbean database (Cuba and French West Indies) were used to determine the progression of disability and to identify clinical predictors of death. **Results** Median age at onset of RNMO was 29.5 years (range 11–74). Median duration of disease was 9.5 years (1–40). Median relapse rate was 0.7 attack/patient/year (0.1–3). 66 patients experienced severe visual loss in at least one eye and 46 in both eyes. Median time from onset to unilateral and bilateral severe visual loss was 3 and 15 years, respectively. Median times to reach Kurtzke Disability Status Scale 3, 6 and 8 from onset of RNMO were 1, 8 and 22 years. There were 24 deaths (25%); within 5 years in 63% of cases. A higher attack frequency during the first year of disease ($p = 0.009$), blindness ($p = 0.04$) and sphincter signs at onset ($p = 0.02$) and lack of recovery of first attack ($p = 0.003$) were independently associated with a shorter time to death. **Conclusion** RNMO is a very rapidly disabling disease affecting primarily young women. This study has identified clinical features that predict a poor outcome. These findings suggest that early and aggressive immunotherapy might be warranted in RNMO.

Silent celiac disease in a cohort of healthy adults. Galván JA, Lemos G, Fernández de Cossio ME, Ruenes C, Martínez Y, Tejada Y, et al. *Autoimmunity*. 2009 Nov;42(8):705–8.

Background Recent studies suggest that celiac disease (CD) is common in many developing countries. Because the disease may be under diagnosed in Cuba, we studied the presence of the disease in a group of apparently healthy adult. **Aims/hypothesis** It was to assess for the first time, the presence of silent CD in a cohort of healthy Cuban adults individuals and to evaluate the tools for diagnosis of CD in this group. **Methods** A total of 200 healthy Cuban adult from Havana City were evaluated. Tissue transglutaminase antibodies (tTGA) were determined by one-step immunochromatographic assay and by commercial ELISA kit. CD specific human leukocyte antigen (HLA) typing was performed by polymerase chain reaction amplification, using sequence-specific primers. In the subject positive for tTGA, the CD was confirmed by intestinal biopsy. **Results** From the 200 studied individuals, only one subject was identified as positive by both assays, being submitted to duodenal biopsy. Morphological changes consistent with CD were found and also supported by HLA-DQ2 (*HLA-DQA1*0501-DQB1*02*). In the follow-up after one year, histological recovery was assessed by a second intestinal biopsy and the serological marker became negative. **Conclusions** This study confirms the existence of silent CD among healthy adult in Cuba and highlights the importance of mass screening for this disease among them. The one-step immunochromatographic assay is a good tool for this purpose.

Simultaneous Isolation of Mycobacterium gastri and Mycobacterium tuberculosis in a Patient With Human Immunodeficiency Virus Infection. de Armas Y, Capó V, Mederos L, Díaz R, Hengge U. *Infectious Diseases in Clinical Practice*. 2009 Sep;17(15):344–5.

AB Typical and atypical mycobacterial infections show a dramatic increase among acquired immune deficiency syndrome patients despite highly-active antiretroviral therapy. The diagnostic challenge is to identify both typical and atypical strains from patient materials in a reasonable time. Here, we present the first case in which both *Mycobacterium gastri* and *Mycobacterium tuberculosis* were isolated in the same specimen (ie, sputum).

Spatial analysis of breast and cervical cancer incidence in small geographical areas in Cuba, 1999–2003. Lorenzo-Luaces Álvarez P, Guerra-Yí ME, Faes C, Galán Álvarez Y, Molenberghs G. *Eur J Cancer Prev*. 2009 Sep;18(5):395–403.


According to the data from the National Cancer Registry, breast and cervical cancer are the two most common nonskin cancers in Cuban

woman. This study was addressed to describe the geographical variation of their incidence at small area level over the period 1999–2003. For each municipality, standardized incidence ratios were calculated and smoothed using a Poisson-Gamma, Poisson-Lognormal and a Conditional Autoregressive (CAR) model. The covariate 'urbanization level' was included in the Poisson-Lognormal and CAR models. The posterior probability of each municipality's relative risk (RR) exceeding unity was computed. Clusters were confirmed using the spatial scan statistic of Kulldorff. The CAR model provided the best fit for the geographical distribution of breast and cervical cancer in Cuba. For breast cancer, a high-risk region was identified in municipalities of Ciudad de La Habana province (CAR-smoothed RR between 1.21 and 1.26). Cervical cancer exhibited two areas with excess risk in the east and extreme west of the island (CAR-smoothed RR range 1.2–2.01 both areas together). Clusters were confirmed only for cervical cancer ($P = 0.001$ for the most likely cluster and $P = 0.003$ for a secondary cluster). In conclusion, the study supports the hypothesis of a spatial variation in risk at small area level essentially for cervical cancer and also for breast cancer that probably reflects the territorial dis-

tribution of life style and socioeconomic factors. This is the first attempt to introduce this methodology in the framework of the National Cancer Registry of Cuba and we expect to extend its use to forthcoming analyses.

Treatment of advanced, recurrent, resistant to previous treatments basal and squamous cell skin carcinomas with a synergistic formulation of interferons. Open, prospective study. Anasagasti-Angulo L, García-Vega Y, Barcelona-Pérez S, López-Saura P, Bello-Rivero I. BMC Cancer. 2009 Jul 30;9:262.

Background Aggressive non-melanoma skin cancer (deeply infiltrating, recurrent, and morphea form lesions) are therapeutically challenging because they require considerable tissue loss and may demand radical disfiguring surgery. Interferons (IFN) may provide a non-surgical approach to the management of these tumors. The aim of this work was to evaluate the effect of a formulation containing IFNs- α and - γ in synergistic proportions on patients with recurrent, advanced basal cell (BCC) or squamous cell skin carcinomas (SCSC). **Methods** Patients with extensive, recurrent, resistant to

other procedures BCC or SCSC received the IFN formulation peri- and intralesionally, three times per week for 3 weeks. They had been previously treated with surgery and/or radiotherapy or chemotherapy. Thirteen weeks after the end of treatment, the original lesion sites were examined for histological evidence of remaining tumor. **Results** Sixteen elder (median 70 years-old) patients were included. They boreed 12 BCC and 4 SCSC ranging from 1.5 to 12.5 cm in the longest dimension. At the end of treatment 47% CR (complete tumor elimination), 40% PR (>30% tumor reduction), and 13% stable disease were obtained. None of the patients relapsed during the treatment period. The median duration of the response was 38 months. Only one patient with complete response had relapsed until today. Principal adverse reactions were influenza-like symptoms well known to occur with interferon therapy, which were well tolerated. **Conclusion** The peri- and intralesional combination of IFNs- α and - γ was safe and showed effect for the treatment of advanced, recurrent and resistant to previous treatments of BCC and SCSC in elder patients. This is the first report of such treatment in patients with advanced non-melanoma skin cancer. The encouraging result justifies further confirmatory trials. 



**4th Pan-American
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Havana, Cuba
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