

## ◆ MANUSCRITO ORIGINAL

# Incidence of inflammatory bowel disease in five geographical areas of Uruguay in the biennial 2007-2008

Gaby Buena vida,<sup>1</sup> Andrea Casañas,<sup>2</sup> Cecilia Vásquez,<sup>2</sup> Magdalena De Souza,<sup>2</sup> Laura Martínez,<sup>2</sup> Inés Gardil,<sup>2</sup> Anaulina Silveira,<sup>3</sup> Beatriz Iade<sup>2</sup>

<sup>1</sup> Medical Education Department, School of Medicine, National University.

<sup>2</sup> Gastroenterology Clinic Prof Dr Henry Cohen, Health Clinic.

<sup>3</sup> Department of Quantitative Methods, School of Medicine, National University, Montevideo, Uruguay.

In the name of the National Inflammatory Bowel Disease Registry (Gastroenterology Clinic Prof Dr Henry Cohen, Health Clinic; School of Medicine; Uruguayan Society of Gastroenterology).

*Acta Gastroenterol Latinoam* 2011;41:281-287

### Summary

**Introduction.** The incidence of inflammatory bowel disease (IBD) is different according to the geographical areas. No data on the incidence of IBD in Uruguay are available. **Objective.** To determine the incidence of IBD, ulcerative colitis (UC) and Crohn's disease (CD), in five areas of Uruguay and to compare the results with those from other geographical regions.

**Material and method.** A prospective study was performed in five areas of Uruguay during 2007-2008. The study population included 645,695 inhabitants. Multiple independent sources were used for the uptake of cases. Patients older than 14 years and living in the selected areas were included only after reviewing their medical history. Confirmed IBD was defined by a standard protocol after one year of follow up. **Results.** A total of 34 cases were diagnosed in the study period, 29 UC and 5 CD. Crude incidence rate for IBD was 2.63 per 100,000 inhabitants/year, 2.25 and 0.39 for UC and CD, respectively. Adjusted rates were 4.26 per 100,000 inhabitants/year for UC and 0.74 per 100,000 inhabitants/year for CD. The UC/CD ratio was 5.8. The average age for IBD was 40.7 years. No statistically significant differences were found between UC and CD by age ( $P = 0.267$ ) or gender ( $P = 0.489$ ). **Conclusions.** Incidence rates of IBD place Uruguay in the regions of low incidence. As it has been described in low-incidence countries, UC

is more common than CD. This study establishes a precedent to follow the evolution of IBD epidemiology in Uruguay.

**Key words.** Epidemiology, incidence, inflammatory bowel disease, ulcerative colitis, Crohn's disease.

### Incidencia de la enfermedad inflamatoria intestinal en cinco zonas geográficas de Uruguay en el bienio 2007-2008

#### Resumen

**Introducción.** La incidencia de la enfermedad inflamatoria intestinal (EII) es diferente según las zonas geográficas. No hay datos disponibles sobre la incidencia de EII en Uruguay. **Objetivo.** Determinar la incidencia de EII, colitis ulcerosa (CU) y enfermedad de Crohn (EC) en cinco áreas de Uruguay y comparar los resultados con los de otras regiones geográficas. **Materiales y método.** Se realizó un estudio prospectivo en cinco regiones de Uruguay durante el bienio 2007-2008. La población del estudio incluyó 645.695 habitantes. Varias fuentes independientes se utilizaron para la captación de los casos. Los pacientes mayores de 14 años que viven en las áreas seleccionadas se incluyeron solo después de la revisión del historial médico. La EII fue definida por un protocolo estándar y confirmada después de un año de seguimiento. **Resultados.** Un total de 34 casos fueron diagnosticados en el período de estudio, 29 de CU y 5 de EC. La tasa bruta de EII fue de 2,63 por 100.000 habitantes/a-

**Correspondence:** Beatriz Iade  
Paraguay 1011/1405 Montevideo. PC 11100.  
Tel./Fax (598) 2400 85 95  
E-mail: beatriz.iade@gmail.com

ño, 2,25 y 0,39 para CU y EC; respectivamente. Las tasas ajustadas fueron de 4,26 por 100.000 habitantes/año para la CU y 0,74 por 100.000 habitantes/año para la EC. La relación CU/EC fue 5,8. La edad media de la EII fue de 40,7 años. No se observaron diferencias estadísticamente significativas entre CU y EC por edad ( $P = 0,267$ ) o sexo ( $P = 0,489$ ). **Conclusiones.** Las tasas de incidencia de EII sitúan a Uruguay en las regiones de baja incidencia. Como se ha descrito en los países de baja incidencia, la CU es más común que la EC. Este estudio establece un precedente para seguir la evolución de la epidemiología de la EII en Uruguay.

**Palabras claves.** Epidemiología, incidencia, enfermedad inflamatoria intestinal, colitis ulcerosa, enfermedad de Crohn.

#### Abbreviations:

IBD: Inflammatory bowel disease.

UC: Ulcerative colitis.

CD: Crohn's disease.

RNEII: The National IBD Registry.

CI: Confidence intervals.

Inflammatory bowel diseases (IBD) are comprised by two major phenotypes: Crohn's disease (CD) and ulcerative colitis (UC). The etiology of IBD remains obscure. The most widely accepted pathophysiologic theory is that inflammation of the mucosa occurs as a consequence of exposure to certain environmental triggers in genetically predisposed individuals. Epidemiological studies may yield clues to the etiology of IBD and provide important information about their natural history. In addition, these studies provide important information to health systems about the costs of care of these chronic diseases.<sup>1-3</sup>

The incidence and prevalence of IBD differ according to the geographical region and socio-demographic characteristics of the population and vary over time. Error! Bookmark not defined.<sup>3</sup> The increase of IBD globally observed since the 50's underscores the epidemiology of IBD as a dynamic process and suggests that environmental factors play a significant role in the etiology.<sup>4</sup> Initially, this increase was more remarkable in developed, industrialized and urbanized regions, such as North America and northern Europe. IBD was rare in other continents, except Israel, Australia and South Africa.<sup>5-7</sup>

This finding led to the "North-South gradient" theory, which suggests that different lifestyles and environmental factors could play a role in the etiology of these diseases.

Over time, the incidence and prevalence of UC and CD have stabilized in areas of high incidence. In contrast, areas with previous low incidence, as South and East Europe, are now reporting a steady increase that makes the differences milder.<sup>3,8-10</sup>

Data of the last decade show that IBD is no longer uncommon also in Asia. This finding suggests that this phenomenon may be related to westernized lifestyles, including improved sanitation and industrialization. However, Crohn's disease remains less frequent than UC in most of these areas.<sup>9,11-14</sup>

In Latin America there are few data on IBD epidemiology and most of the available information is based on hospital and retrospective records.<sup>15-17</sup> A research about the incidence of inflammatory disease in Argentina and Panama performed between 1987-1993 have placed them as low incidence areas, especially for CD.<sup>18</sup> More recent studies show an increasing trend, with figures mirroring the evolution followed by IBD in high incidence areas.<sup>16,17,19,20</sup> In Uruguay, the only available data until 2007 were based on casuistics.<sup>21-23</sup>

The aim of the present study was to determine the incidence of IBD, UC and CD, in five areas of Uruguay and to compare the results with those from other geographical regions. Obtained data will be of interest to our country and will help deepen our knowledge about IBD natural history.

## Material and methods

### Population

Uruguay is a country in South America, that stretches over 176,215 km<sup>2</sup> and has a total population of 3,241,003 inhabitants. The country is divided in 19 regions called Departments, from which the capital city Montevideo houses half of the population. Ninety per cent of the population is urban (Figure 1).<sup>24</sup>

The immense majority of Uruguayans have Spanish and Italian origins, followed by French, German and other European origins; 87.4% of the population is Caucasian, 9.1% are Afro-descendants and 2.9% are aborigines. Male/female ratio is 0.93.<sup>25</sup> The levels of demographic variables follow the same tendencies as those observed in developed countries.<sup>26</sup>

**Figure 1.** Location of Uruguay in the region and of each area studied in Uruguay.



Access to drinking water, education and sewage services is almost universal. The 2004 Census<sup>25</sup> showed that 97.2% of the population living in towns of 5,000 or more inhabitants has some kind of medical care coverage.

According to 2007 data from the United Nations Program for Development, Uruguay ranked third in Latin America and 50th among 182 countries, with a Human Development Index (HDI) of 0.865.<sup>27</sup> However, contrarily to most countries with a high HDI, in Uruguay, as in the rest of Latin America, there are more pronounced gaps in each aspect.<sup>28</sup>

The National IBD Registry (RNEII, for its Spanish acronym) was created in 2006 and in 2008 it was declared of ministerial interest by the Ministry of Health (Ministerial Order 222 dated April 28<sup>th</sup>, 2008, Ref No. 001-3-1269/2008). This order applies to all medical institutions, whether public or private. After this, it was quite easy to obtain all the information required from the medical centers to identify new cases (data from endoscopy files, pathology, pharmacy and doctors). The RNEII collects and updates data of all patients diagnosed with IBD across the country. This information is provided by the physicians. At least once a year each patient's information is updated through communication with the doctor and/or the patient. The RNEII includes data as IBD type, gender, age and place of residence at onset.

#### Targeted areas

To select a geographical area (department), it

was required a health care service facility capable of diagnosing new cases (with gastroenterologists, endoscopists and pathologists) and gastroenterologists trained in the use of RNEII for enrollment and confirmation of cases. The environmental and socio-demographic features of the different areas were also considered. For example, Artigas and Salto are in the North, and Lavalleja and San José, in the South. Montevideo, the national capital city, was also selected. The first three departments have a population density of 6 to 15 inhabitants per km<sup>2</sup>, San José 15 to 35 inhabitants per km<sup>2</sup> and Montevideo over 35 inhabitants per km<sup>2</sup>.

In order to obtain the total incident cases, centers with incomplete available information were excluded. In Salto, the information was collected from the only private health care center. In Montevideo, two health care centers, a public and a private hospital, were considered. For Artigas, Lavalleja and San José, the population of the 2004 census was considered and the population of towns that use medical services from neighbor areas was excluded. Finally, we included the following populations to calculate incidences: Artigas 78,019 inhabitants (minus Bella Union, 13,187 inhabitants), Lavalleja 60,925 inhabitants (minus José P. Varela, 5,332 inhabitants), San José 103,104 inhabitants (minus Ciudad del Plata, 23,110 inhabitants), Salto 49,460 members of CAM Private Health Care Center, and Montevideo 395,816 persons receiving medical attention at University Hospital and Impasa Health Center. The total population included was 645,695 individuals.

#### Inclusion and exclusion criteria

The study included both outpatients and inpatients, older than 14 years and residents in the selected areas for at least one year before diagnosis, with a new case of IBD (UC or CD) diagnosed from January 1<sup>st</sup>, 2007 to December 31<sup>st</sup>, 2008 either they had surgery or not. Patients were excluded from the study if the disease had started elsewhere, the diagnosis was not confirmed after one year or the colitis was unclassified.

Multiple and independent sources were used to ensure the most thorough detection of potential cases and to determine the same event.<sup>29,30</sup> The active search included endoscopy, pathology, general archives and hospitals' pharmacy archives. After

the potential case was identified, an appointment to attend the clinic was given to the patient, a RNEII form was filled in and the patient's consent was obtained. To avoid any changes in the diagnosis, the case was confirmed by the principal investigator of each area one year after the initial diagnosis by reviewing the medical record. The standard protocol for diagnosis and definition of IBD was used.<sup>31,32</sup>

### Statistical method

The global and specific IBD incidence rates were calculated as the number of new cases for the total population selected, using  $k = 100,000$  inhabitants and one year as the time unit. We used the direct method for standardization (Waterhouse's definition for standard population age interval from 15 to 64 years, by gender) to remove the confounding effect caused by age and gender distribution in the populations to be compared.<sup>33,34</sup> For the calculation of 95% confidence Intervals (CI), the numerators were considered to have a Poisson distribution and the denominators were assumed to be constant. A Fisher's exact test was used to compare calculated proportions and to determine statistical significance ( $P$  value < 0.05).

### Ethics

This present study was conducted within the RNEII framework. The RNEII was approved by the School of Medicine's Ethics Committee.

### Results

The population of the studied areas is 645,695 people (336,540 females and 309,155 males) and it represents 20% of the country's total population. Thirty-four new cases of IBD were diagnosed, 29 UC and 5 CD, 21 females and 13 males (Table 1). The UC/CD ratio was 5.8.

The crude incidence rate for IBD was 2.63 per 100,000 inhabitants/year (3.12 for females and 2.10 for males). The incidence rate for UC was 2.25 per 100,000 inhabitants/year (2.53 for females and 1.94 for males) and for CD, 0.39 per 100,000 inhabitants/year (0.59 for females and 0.16 for males). The adjusted incidence rate for IBD after standardization was 4.01 per 100,000 inhabitants/year. For UC this rate was 4.26 per 100,000 inhabitants/year (95% CI 3.54-4.98) and

for CD, 0.74 per 100,000 inhabitants/year (95% CI 0.56-0.92) (Table 2).

The average age at the moment of IBD diagnosis was 40.7 + 2.5 years, with a median age of 43 years and a range from 15 to 67 years. The average age at diagnosis was 41.7 + 2.8 years for UC (95% CI 35.98-47.33, median 42 years, range 15 to 67 years). The average age at diagnosis was 35.4 + 6.1 years for CD (95% CI 18.45-52.35, median of 44 years, range 20 to 47 years). Ages and gender of UC and CD were not statistically different ( $P = 0.267$  and 0.489, respectively) (Table 2).

**Table 1.** Number of cases by sex and year.

Diagnosis after follow-up	Year of diagnosis		Sex		
			Females	Males	Total
UC	Year of diagnosis	2007	9	6	15
		2008	8	6	14
	Total	17	12	29	
CD	Year of diagnosis	2007	3	1	4
		2008	1	0	1
	Total	4	1	5	
UC+ CD	Total		21	13	34

UC: ulcerative colitis, CD: Crohn's disease

**Table 2.** Incidence rates of IBD by age and sex.

Age	All			Females			Males		
	n	IR	SIR	n	IR	SIR	n	IR	SIR
15 - 24	9	4.53	5.01	7	11.82	7.48	2	2.01	2.33
25 - 34	2	1.09	1.14	1	1.07	1.09	1	1.12	1.19
35 - 44	7	4.24	3.33	4	4.72	3.65	4	5.02	3.97
45 - 54	9	6.17	5.16	6	7.82	6.6	3	4.29	3.57
55 - 64	6	5.22	5.34	3	4.84	5.12	3	5.58	5.58

n: number of cases, IR: crude incidence rate, SIR: standardized incidence rate following the global standard population as defined by Waterhouse.

### Discussion

This first study of IBD incidence conducted in five areas of Uruguay during the 2007-2008 period shows a crude rate of 2.63 per 100,000 inhabitants/year for IBD (2.25 per 100,000 inhabitants/year for UC and 0.39 per 100,000 inhabitants/year for

CD). Based on the global epidemiology studies, these data place Uruguay in a low incidence area.<sup>35</sup> We do not believe that this low incidence is due to cases missed from capture, since the included centers were few but well equipped for the diagnosis and multiple data sources were used. Furthermore, in a pilot study conducted from June 2006 to June 2007, the prevalence of IBD in 5 areas was 13 per 100,000 inhabitants (range 8.9 to 19.9).<sup>36</sup>

The incidence of IBD has shown variations along time. Today, in countries presenting high incidence, the increase in the UC incidence precedes the increase in the CD incidence by about 15 to 20 years.<sup>37</sup> Subsequent studies in Eastern Europe have showed a similar behavior, maintaining an initial increase of UC followed by an increase of CD, as those areas reach incidence and prevalence rates similar to those observed in the North.<sup>38</sup> The 5.8 ratio between UC and CD incidence rates in our study is comparable to that in the regions that showed low incidence.

Latin America also shows an increase of IBD through the decades. In the population study conducted in Panama by Linares de la Cal et al between 1987 and 1993, the incidence of UC was 1.2 per 100,000 inhabitants, with no cases of CD. In Argentina the figures were 2.2 per 100,000 inhabitants for UC and 0.03 per 100,000 inhabitants for CD.<sup>18</sup> In Puerto Rico, Appleyard et al described a significant increase in the incidence of IBD between 1996 and 2000 (3.07 to 7.74 per 100,000 inhabitants), being significantly higher for CD (4-fold increase) but not for UC (1.7 fold increase).<sup>39</sup> In the prospective study conducted from 1997 to 1999 in Martinique and Guadalupe, two Caribbean islands, by Eduard et al, using the same EPIMAD survey system applied in France, the incidence was 2.44 and 1.95 per 100,000 inhabitants for UC and CD, respectively.<sup>40</sup> Victoria et al retrospectively captured the cases of a reference center in the state of Sao Paulo (Brazil) and followed them from 1980 to 2005. They observed an increase in the initial incidence of UC from 0.74 per 100,000 inhabitants during the 1986-1990 period to 6.76 per 100,000 inhabitants during the 1996-2000 period, with a drop to 4.48 per 100,000 inhabitants during the 2000-2004 period. CD incidence increased throughout the whole period, starting with 0.24 per 100,000 inhabitants and reaching 3.5 per 100,000 inhabitants in the last five years.<sup>20</sup> In a prospective

follow-up study from Barbados, another Caribbean island, Edwards *et al* observed an increase of the incidence in time, although this increase was not steady. UC incidence was 1.3 per 100,000 inhabitants during the 1980-1984 period, 2.3 per 100,000 inhabitants during the 1995-1999 period and 1.6 per 100,000 inhabitants during the 2000-2004 period. CD followed a similar behavior, increasing from 0.3 per 100,000 inhabitants during the 1980-1984 period to 1.3 per 100,000 inhabitants during the 1990-1994 period and dropping afterwards to 0.6 per 100,000 inhabitants.<sup>41</sup> In brief, these studies reveal that the incidence in South America, Central America and the Caribbean is very variable, with figures below those reported in high incidence countries. However, considering the studies performed in the last years, it is higher than in Uruguay, especially for CD.

This global tendency has led to relating the increase in the IBD incidence with life style changes that occur when societies get westernized or industrialized. Furthermore, the pattern observed in the high incidence areas is repeated in Latin America, where UC precedes and exceeds CD with a gap tending to be reduced along the time. It is not clear why Uruguay presents figures comparable to those observed in early years in Europe. If genetic factors were the strongest determinants of IBD, the figures in Uruguay should be similar to those in Spain or Italy, but this fact was not observed in our study.<sup>9,42,43</sup>

In the present study, IBD was found more frequently in women than in men, which is consistent with most reports, including those in South America and the Caribbean.<sup>9,36,42,43</sup> About the average age at diagnosis, it was somewhat higher than that reported in the region. This paper shows that the average age at the time of diagnosis was lower for CD than for UC, as reported by other publications.<sup>40</sup>

We conclude that the incidence rates observed in Uruguay place the country among the low incidence regions. As it has been described in low-incidence countries, UC is more common than CD. This study establishes a precedent to follow the evolution of IBD changing epidemiology in Uruguay.

**Acknowledgements.** *We wish to thank doctors, endoscopists and pathologists of each participating center for their enthusiastic cooperation in the identification of patients, Dr Henry Cohen for his inestimable support,*

*Valeria Gradin for her assistance and Abbott Laboratories Uruguay S.A for the financial support.*

## References

- Registros de Cáncer. Principios y métodos IARC. Publicación científica N° 95. Lyon Francia. 1995. OMS.
- Piedrola G. Medicina Preventiva y Salud Pública. 10ª Ed. Barcelona: Masson. S.A, 2001:177-182.
- Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004;126:1504-1517.
- Loftus CG, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Tremaine WJ, Melton LJ 3rd, Sandborn WJ. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. *Inflamm Bowel Dis* 2007;13:254-261.
- Shivananda S, Lennard-Jones J, Logan R, Fear N, Price A, Carpenter L, van Blankenstein M. Incidence of inflammatory bowel disease across Europe: Is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). *Gut* 1996;39:690-697.
- Shivananda S, Peña AS, Mayberry JF, Ruitenber EJ, Hoedemaeker PJ. Epidemiology of proctocolitis in the region of Leyden, The Netherlands. A population study from 1979-1983. *Scand J Gastroenterology* 1987;22:993-1002.
- Loftus EV Jr, Sandborn WJ. Epidemiology of inflammatory bowel disease. *Gastroenterol Clin North Am* 2002;31: 1-20.
- Hinojosa J, Primo J, Lledó S, López A, Roig JV, Fernández J. Incidence of inflammatory bowel disease in Sagunto. *Rev Esp Enferm Dig* 1990;78:283-287.
- Lakatos PL. Recent trends in the epidemiology of inflammatory bowel diseases: up or down? *World J Gastroenterol* 2006;12:6102-6108.
- López-Serrano P, Pérez-Calle JL, Carrera-Alonso E, Pérez-Fernández T, Rodríguez-Caravaca G, Boixeda-de-Miguel D, Fernández-Rodríguez CM. Epidemiologic study on the current incidence of inflammatory bowel disease in Madrid. *Rev Esp Enferm Dig* 2009;101:768-772.
- Sood A, Midha V, Sood N, Bhatia AS, Avasthi G. Incidence and prevalence of ulcerative colitis in Punjab, North India. *Gut* 2003;52:1587-1590.
- Al-Ghamdi AS, Al-Mofleh IA, Al-Rashed RS, Al-Amri SM, Aljebreen AM, Isnani AC, El-Badawi R. Epidemiology and outcome of Crohn's disease in a teaching hospital in Riyadh. *World J Gastroenterol* 2004;10:1341-1344.
- Goh K, Xiao SD. Inflammatory bowel disease: a survey of the epidemiology in Asia *J Dig Dis* 2009;10:1-6.
- Thia KT, Loftus EV Jr, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. *Am J Gastroenterol* 2008;103:3167-3182.
- Gaburri PD, Castro LEVV, Ferreira JOD, Lopes MHM, Ribeiro AMB, Alves RA, Froede EC, Oliveira KS, Gaburri AK, Gaburri D, Meirelles GSP, Souza AFM, Chebli JMF. Epidemiology, clinical features and evolution of Crohn's disease: a study of 60 cases. *Arq Gastroenterol* 1998;35:240-246.
- Souza MH, Troncon LE, Rodrigues CM, Viana CF, Onofre PH, Monteiro RA, Passos AD, Martinelli AL, Meneghelli UG. Trends in the occurrence (1980-1999) and clinical features of Crohn's disease and ulcerative colitis in a university hospital in the southeastern Brazil. *Arq Gastroenterol* 2002;39:98-105.
- Figueroa CC, Quera PR, Valenzuela EJ, Jensen BC. Inflammatory bowel disease: experience of two Chilean centers. *Rev Med Chile* 2005;133:1295-1304.
- Linares de la Cal JA, Cantón C, Hermida C, Pérez-Miranda M, Maté-Jiménez J. Estimated incidence of inflammatory bowel disease in Argentina and Panamá (1987-1993). *Rev Esp Enferm Dig* 1999;91:277-286.
- Torres EA, De Jesús R, Pérez CM, Iñesta M, Torres D, Morrell C, Just E. Prevalence of inflammatory bowel disease in a insured population in Puerto Rico during 1996. *P R Health Sci J* 2003;22:253-258.
- Victoria CR, Sassak LY, Nunes HR. Incidence and prevalence rates of inflammatory bowel diseases, in Midwestern of São Paulo State, Brazil. *Arq Gastroenterol* 2009; 46:20-25.
- Gutiérrez Blanco H, Gutiérrez Galiana H, Nin Sacarello R. Enfermedad de Crohn: a propósito de 85 casos. *Prensa Med Uruguay* 1984;7:75-79.
- Iade B, Bianchi C, Espíndola F. Características clínicas de presentación y seguimiento de una cohorte de 121 pacientes con colitis ulcerosa crónica en Uruguay. *Rev Med Uruguay* 2005;21:298-302.
- Iade B, Bianchi C, Espíndola F. Características clínicas de presentación y evolutivas de una cohorte de 48 pacientes con enfermedad de Crohn en Uruguay. *Rev Med Uruguay* 2005;21:303-307.
- Instituto Nacional de Estadística de Uruguay. Censo de población y hogares 2004. <http://www.ine.gub.uy>.
- Instituto Nacional de Estadística de Uruguay. Encuesta Nacional de Hogares Ampliada 2006. <http://www.ine.gub.uy/enha2006/informestematicos.asp>.
- Pellegrino A. Caracterización demográfica del Uruguay. [http://www.anep.edu.uy/historia/clases/clase20/cuadros/15\\_Pellegrino-Demo.pdf](http://www.anep.edu.uy/historia/clases/clase20/cuadros/15_Pellegrino-Demo.pdf).
- Programa de las Naciones Unidas para el Desarrollo (PNUD). Informe mundial sobre desarrollo humano 2009. <http://www.undp.org.uy>
- Programa de las Naciones Unidas para el Desarrollo (PNUD). Desarrollo humano en Uruguay 2008. <http://www.undp.org.uy>.
- International Working Group for Disease Monitoring and Forecasting. Capture-recapture and multiple-record systems estimation. I. History and theoretical development. *Am J Epidemiol* 1995;142:1047-1058.
- International Working Group for Disease Monitoring and Forecasting. Capture-recapture and multiple-record systems estimation. II. Applications in human diseases. *Am J Epidemiol* 1995;142:1059-1068.
- Stange EF, Travis SPL, Vermeire S, Reinisch W, Geboes K, Barakauskiene A, Feakins R, Fléjou JF, Herfarth H, Hommes DW, Kupcinskis L, Lakatos PL, Mantzaris GJ, Schreiber S, Villanacci V, Warren BF. European evidence-based consensus on the diagnosis and management of ulcerative colitis: definitions and diagnosis *J Crohns Colitis* 2008;2:1-23.

32. Stange EF, Travis SP, Vermeire S, Beglinger C, Kupcinskas L, Geboes K, Barakauskiene A, Villanacci V, Von Herbay A, Warren BF, Gasche C, Tilg H, Schreiber SW, Schölmerich J, Reinisch W, European Crohn's and Colitis Organization. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Gut* 2006;55:1-15.
33. Waterhouse J, Muir CS, Correa P, Powell J, eds. Cancer incidence in five continents, Vol III. IARC Scientific Publications (Lyon), 1976.
34. Organización Panamericana de la Salud. Salud en las América: edición 2002, Vol 1. Washington DC OPS; 2002.
35. Saro C, Sicilia B. Inflammatory bowel diseases: a disease(s) of modern times? Is incidence still increasing? *World J Gastroenterol* 2008;14:5491-5498.
36. Iade B, Buenavida G, Caviglia C. Epidemiology of the inflammatory bowel disease in Uruguay (abstract). *J Crohns Colitis* 2008;2 (suppl 1):75-76.
37. Fonager K, Sørensen HT, Olsen J. Change in incidence of Crohn's disease and ulcerative colitis in Denmark. A study based on the National Registry of Patients, 1981-1992. *Int J Epidemiol* 1997;26:1003-1008.
38. Lakatos L, Lakatos PL. Is the incidence and prevalence of inflammatory bowel diseases increasing in Eastern Europe? *Postgrad Med J* 2006;82:332-337.
39. Appleyard CB, Hernández G, Rios-Bedoya CF. Basic epidemiology of inflammatory bowel disease in Puerto Rico. *Inflamm Bowel Dis* 2004;10:106-111.
40. Eduard A, Paillaud M, Merle S, Orhan C, Chenayer-Panelatti Dagger M, COGEAG. Incidence of inflammatory bowel disease in the French West Indies (1997-1999). *Gastroenterol Clin Biol* 2005;29:779-783.
41. Edwards CN, Griffith SG, Hennis AJ, Hambleton IR. Inflammatory bowel disease: incidence, prevalence, and disease characteristics in Barbados, West Indies. *Inflamm Bowel Dis* 2008;14:1419-1424.
42. Ranzi T, Bodini P, Zambelli A, Politi P, Lupinacci G, Campanini MC, Dal Lago AL, Lisciandrano D, Bianchi PA. Epidemiological aspects of inflammatory bowel disease in a North Italian population: a 4-year prospective study. *Eur J Gastroenterol Hepatol* 1996;8:657-661.
43. Tragnone A, Corrao G, Miglio F, Caprilli R, Assuero Lanfranchi G, Gruppo Italiano per lo Studio del Colon e del Retto (GISC). Incidence of Inflammatory Bowel Disease in Italy: a nationwide population-based study. *Int J Epidemiol* 1996;25:1044-1052.