Antibiotic susceptibility of *Streptococcus pneumoniae* colonizing the nasopharynx of Colombian children with pneumonia[1]

Aura Lucía Leal[2] *and Elizabeth Castañeda*[2]

ABSTRACT Streptococcus pneumoniae *is one of the principal causal agents of acute respiratory infection (ARI) in children, and its resistance to antibiotics has increased worldwide. This study examined the patterns of susceptibility to antibiotics of* S. pneumoniae *that had colonized the upper respiratory tract of 272 children hospitalized for pneumonia in two hospitals in Santafé de Bogotá.* S. pneumoniae *was isolated from 114 patients (42%). Diminished susceptibility to penicillin was noted in 19 isolates (17%), with 12 (11%) having an intermediate level of sensitivity and 7 (6%) showing outright resistance. Only 1 of the 19 isolates resistant to penicillin also showed resistance to ceftriaxone. There was diminished sensitivity to erythromycin in 3 isolates (3%), to chloramphenicol in 6 (5%), and to co-trimoxazole (trimethoprim + sulfamethoxazole) in 46 (40%). Resistance to multiple drugs was found in 7 isolates (6%). The most commonly encountered penicillin-resistant serotype was 23F (68.4%). An association was observed between age, prior use of antibiotics, and colonization by* S. pneumoniae *with reduced penicillin sensitivity or multiple-drug resistance. This study confirmed the presence of antibiotic-resistant* S. pneumoniae *in Colombia and highlights the importance of the rational use of antibiotics and of the implementation of epidemiologic surveillance for this agent.*

Every year in developing countries, some 4.5 million persons, most of them under 5 years of age, die of acute respiratory infections (ARI) (*1*). Most ARI episodes are caused by viral agents and are self-limiting, but the bacterial pneumonias, which occur less frequently, carry a much higher risk of complications and death (*2*).

Streptococcus pneumoniae (pneumococcus) and *Haemophilus influenzae* are the two bacterial pathogens most commonly isolated in pediatric pneumonia (*3*). Since these microorganisms can colonize the upper respiratory tract, aspiration of secretions may lead to pneumonia, especially if an individual's susceptibility to a bacterial infection were increased by malnutrition, viral infection, or other factors that would change the immune response (*4*). Colonization of the upper airways by *S. pneumoniae* can occur during the first few days of life; early colonization is associated with living in a large family and a higher risk of suffering from the disease (*5*).

An etiologic diagnosis of pneumococcal pneumonia is often difficult to establish. *S. pneumoniae* is not easily cultured from blood samples, and invasive diagnostic procedures, such as lung puncture, pose too great a risk for most patients. To cover the possibility of undiagnosed pneumococcal pneumonia, World Health Organization (WHO) guidelines for the management of ARI include empirical use

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[2] National Institute of Health, Santafé de Bogotá, Colombia. Address correspondence to: Elizabeth Castañeda, Laboratorio de Microbiología, Instituto Nacional de Salud, Avenida Eldorado, Carrera 50, Santafé de Bogotá, Colombia (Tel. [57-1] 222-0577, ext. 445 or 446; fax [57-1] 222-0194).

of antimicrobial agents such as procaine penicillin, ampicillin, and co-trimoxazole (trimethoprim + sulfamethoxazole) (*6, 7*).

Worldwide, *S. pneumoniae* has demonstrated increasing resistance to a variety of antibiotics. Studies in Spain and Hungary have documented resistance to penicillin in 44% and 57% of pneumococcal isolates, respectively. The organism is also frequently resistant to co-trimoxazole and chloramphenicol (*8, 9*). The patient's age, the serotypes involved, the time of colonization, rapid recolonization following treatment, prior use of antibiotics, and previous hospitalization are factors that have been found to be associated with the presence of resistant isolates (*8*).

In studies in Pakistan, *S. pneumoniae* serotypes found in the respiratory tract of sick children matched the serotypes in cultures of their blood, and the antibiotic sensitivities of the isolates corresponded in 98% of cases (*10*). Thus, in children with pneumonia, the antimicrobial resistance patterns of the *S. pneumoniae* that cause the invasive disease may be reflected in the nasopharyngeal isolates, a circumstance that would prove useful in implementing epidemiologic surveillance programs in an area. Knowledge of resistance patterns would also allow for better therapeutic case management (*11*).

The objectives of the present study were (a) to investigate the frequency of nasopharyngeal colonization by *S. pneumoniae* in children hospitalized with a diagnosis of pneumonia, (b) to determine these isolates' patterns of resistance to the antibiotics recommended for use in the ARI program, (c) to identify the serotypes of the penicillin-resistant isolates, and (d) to document factors associated with the resistance pattern. Analysis of these data would give an indication of the utility of nasopharyngeal isolates in a surveillance program.

MATERIALS AND METHODS

Patients. The study participants were 272 children under 5 years of age admitted to the Lorencita Villegas de Santos Children's Hospital or La Misericordia Hospital in Santafé de Bogotá between November 1993 and October 1994. All met WHO diagnostic criteria for pneumonia or severe pneumonia: a fast respiration rate (>60 breaths per minute in infants under 2 months of age, >50 in infants aged 2 months to 1 year, or >40 in children over 1 year), and, for severe pneumonia, the additional presence of retractions of the suprasternal notch or costal margins, indicating respiratory distress (*6*). Inclusion in the study also required a clinical evolution of less than 15 days. Patients with symptoms of stridor or croup (acute laryngotracheobronchitis) were excluded. For each child, age, prior use of antibiotics, respiratory rate, presence or absence of retractions, and clinical diagnosis were recorded on a form.

Specimen, isolation, and identification. A specimen of nasopharyngeal secretion was obtained from each patient using a flexible Dacron swab and seeded directly onto a trypticase soy agar supplemented with 5% sheep's blood and 5 μg/mL gentamicin (*12*). Specimens were incubated at 37 ºC for 20 to 24 hours in an atmosphere containing 2% to 5% CO_2 (candle jar method). *S. pneumoniae* identification was based on macroscopic and α-hemolytic colony characteristics, microscopic morphology by Gram's stain, optochin sensitivity, and bile solubility (*13*).

Antimicrobial sensitivity. Susceptibility to penicillin was determined using the Kirby-Bauer disk diffusion method, employing a Mueller-Hinton agar containing 5% sheep's blood and 1 μg oxacillin disks (screening test). This same technique was used to determine sensitivity to erythromycin using 15 μg disks, and to chloramphenicol with 30 μg disks. All procedures were performed and analyzed according to the standards set by the National Committee for Clinical Laboratory Standards (NCCLS) of the United States of America (*14*). *S. pneumoniae* ATCC 49619 was used as the control strain.

The minimum inhibitory concentrations (MIC) of penicillin and ceftriaxone were determined in the isolates that exhibited diminished susceptibility to penicillin (diameter of oxacillin inhibition zone <20 mm). MICs of co-trimoxazole were also measured to determine the susceptibility of all isolates to that treatment (*15*). In each case, the microdilution method was used with Mueller-Hinton broth containing 5% horse's blood in accordance with NCCLS specifications (*16*).

Serotyping. The isolates that demonstrated penicillin- or multiple-drug-resistance (defined as resistance to three or more antibiotics)[3] were serotyped by the *quellung* (Neufeld's) reaction using a panel of 12 antisera from the Stantens Seruminstitut in Copenhagen (*17*).

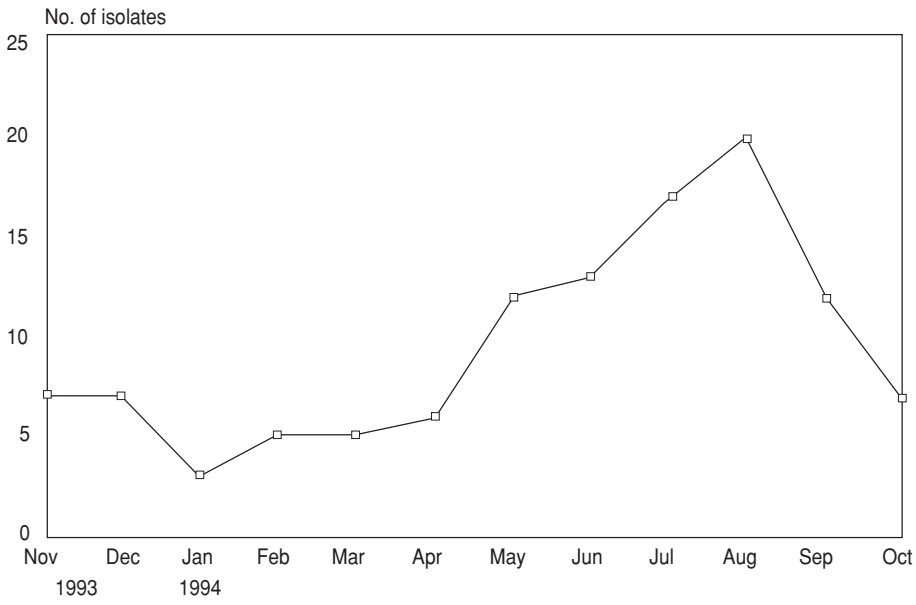
Data analysis. The prevalence of each category of *S. pneumoniae* resistance and the corresponding prevalence ratio (PR) were calculated. Confidence intervals (CI) of 95% for the PR were determined using Epi Info epidemiologic software (*18*).

RESULTS

S. pneumoniae was isolated from 114 of the 272 patients' nasopharyngeal secretions, indicating a minimum colonization rate of 42%. Of the patients in whom colonization was detected, 76 (67%) were male and 38 (33%) female; 94 (82%) were under 3 years of age, and 57 of the latter (61%) were under 1 year old. The average age of *S. pneumoniae* carriers was 1.4 years. The highest prevalence of colonization was at 6 months of age.

[3] In this study, co-trimoxazole, although a combination of trimethoprim and sulfamethoxazole, was considered to be a single antibiotic.

FIGURE 1. Distribution over time of *S. pneumoniae* isolates colonizing the nasopharynx of 114 pediatric patients hospitalized for pneumonia in Santafé de Bogotá



Isolates of *S. pneumoniae* were obtained throughout the year of the study. However, Figure 1 shows that the majority of isolates (65%) were collected between May and September 1994.

Previous antibiotic treatment was documented in 36 (31%) of the 114 children with colonization. Thirty-two (89%) of this subgroup had received a β-lactam antibiotic, either amoxicillin (25), penicillin G (4), amoxicillin and penicillin G (1), or a second-generation cephalosporin (2). Seventy-five children had not received antibiotics. It was impossible to determine whether antibiotics had been administered to three children. Severe pneumonia was diagnosed in 79 patients with colonization (69%).

Reduced sensitivity to penicillin was detected in 19 *S. pneumoniae* isolates (17%) by the oxacillin screen. Oxacillin MICs indicated intermediate sensitivity in 12 isolates (11%) and resistance in 7 (6%). Only one penicillin-resistant strain was also resistant to ceftriaxone. Sensitivity to co-trimoxazole was intermediate in 21 isolates (18%), while 25 isolates (22%) were fully resistant to this agent. Intermediate sensitivity to erythromycin was encountered in two isolates (2%) and resistance was found in one (1%). Chloramphenicol resistance was seen in six isolates (5%) (Table 1).

Thirteen of the 19 *S. pneumoniae* isolates with low sensitivity to penicillin corresponded to serotype 23F, 2 to type 14, 1 to type 19F, and 3 were not typable. The most common serotype among the multiresistant isolates (those with low sensitivity to three or more antibiotics) was 23F (6 out of 7) (Table 2).

Reduced sensitivity to at least one antibiotic was found in 48 isolates (42%). All isolates resistant to penicillin were also resistant to co-trimoxazole. Multiresistance was present in seven isolates (6%), five of which were fully resistant to all of the antibiotics tested. All multiresistant isolates were resistant to penicillin and co-trimoxazole. The most common multiresistance pattern—to penicillin, chloramphenicol, and co-trimoxazole—was present in four isolates (Table 2).

Of the 19 patients carrying *S. pneumoniae* with diminished susceptibility to penicillin or multiple-drug resistance, 12 were boys and 7 were girls. Five were under the age of 1 year, eight were between 1 and 2 years, and six were between ages 3 and 5.

Colonization of the nasopharynx by penicillin-resistant or multiresistant *S. pneumoniae* was found in 5 of the 57 patients under 1 year of age, 8 of the 37 between 1 and 2, and 6 of the 20 between 3 and 5. A positive association was seen between increasing age and the presence of penicillin- or multiple-drug-resistant strains. Compared with children under 1 year of age, those in the 1–2-year age group had a prevalence of resistant isolates

TABLE 1. Antimicrobial susceptibility of nasopharyngeal isolates of *Streptococcus pneumoniae* in 114 pediatric patients hospitalized for pneumonia in Santafé de Bogotá, 1994

	Sensitive isolates		Intermediate sensitivity		Resistant isolates	
Antimicrobial agent	No.	%	No.	%	No.	%
Penicillin[a]	95	83	12	11	7	6
Ceftriaxone[b]	18	95	0	0	1	5
Co-trimoxazole[c]	68	60	21	18	25	22
Erythromycin[d]	111	97	2	2	1	1
Chloramphenicol[e]	108	95	0	0	6	5

[a] Minimum inhibitory concentration (MIC) <0.06 μg/mL in sensitive isolates, between 0.1 and 1 μg/mL in those with intermediate sensitivity, and >2 μg/mL in resistant isolates.
[b] MIC <0.25 μg/mL in sensitive isolates, between 0.5 and 1 μg/mL in those with intermediate sensitivity, and >2 μg/mL in resistant isolates.
[c] MIC (of trimethoprim/sulfamethoxazole) <0.5/9.5 μg/mL in sensitive isolates, between 1/19 and 2/38 μg/mL in those with intermediate sensitivity, and >4/76 μg/mL in resistant isolates.
[d] Disk diffusion interpretation (Kirby-Bauer): more than 21 mm in sensitive isolates, from 16 to 20 mm in those with intermediate sensitivity, and less than 15 mm in resistant isolates.
[e] Disk diffusion interpretation (Kirby-Bauer): more than 21 mm in sensitive isolates, from 18 to 20 mm in those with intermediate sensitivity, and less than 17 mm in resistant isolates.

TABLE 2. Serotypes of *Streptococcus pneumoniae* associated with various patterns of resistance

Serotype	No. of strains isolated	Pattern of resistance
23F	1	Penicillin, ceftriaxone, chloramphenicol, co-trimoxazole (trimethoprim + sulfamethoxazole)
	1	Penicillin, erythromycin, co-trimoxazole
	4	Penicillin, chloramphenicol, co-trimoxazole
	7	Penicillin, co-trimoxazole
14	2	Penicillin, co-trimoxazole
19F	1	Penicillin, erythromycin, co-trimoxazole
Nonserotypable	3	Penicillin, co-trimoxazole
Total	19	

TABLE 3. Characteristics of patients, prevalence, and prevalence ratio (with 95% confidence intervals) for colonization by strains of *Streptococcus pneumoniae* with low sensitivity to penicillin

Groups of patients		Prevalence of resistant strains	Prevalence ratio[a]	95%CI
Sex:	M	12/76	0.9	0.37 to 2.00
	F	7/38	1.0	
Age:	<1 year	5/57	1.0[b]	
	1 to 2 years	8/37	2.5	0.9 to 7.0
	3 to 5 years	6/20	3.5	1.2 to 10.0[c]
Prior antibiotic administration				
	Yes	9/36	2.1	
	No	9/75	1.0	0.9 to 4.8
	Undetermined	1/3		
Clinical diagnosis				
	Pneumonia	2/35	1.0	
	Severe pneumonia	17/79	3.8	0.9 to 15.4

[a] The category in which the prevalence ratio is 1.0 is the reference category.
[b] χ^2 linear tendency, $P < 0.05$.
[c] $P = 0.02$.

2.4 times higher (95%CI: 0.9 to 7.0), while 3–5-year-olds experienced a prevalence 3.4 times higher (95%CI: 1.2 to 10.0). In the latter case, the tendency for the percentage of resistant isolates to increase with age was statistically significant ($P = 0.02$) (Table 3).

Nine of the 36 patients known to have received previous antibiotic treatment were colonized by strains of penicillin-resistant *S. pneumoniae*. In contrast, only 9 of the 75 patients who had not received antibiotics were carriers of resistant isolates. Consequently, the risk of carrying resistant *S. pneumoniae* was 2.1 times greater (95%CI: 0.9 to 4.8) in children with previous antibiotic exposure (Table 3).

In the children who were colonized by penicillin-resistant or multiresistant *S. pneumoniae,* the most common clinical diagnosis was severe pneumonia (17 of 19 cases). The frequency of resistant isolates was 3.8 times higher in cases of severe pneumonia (95%CI: 0.9 to 15.4) (Table 3).

DISCUSSION

Colonization of the upper respiratory tract by *S. pneumoniae* is common, especially in children, but the prevalence rates of colonization found in different studies have varied widely. In some cases the similarity between invasive disease agents and the nasopharyngeal isolates has been confirmed (*10, 11*). Given the difficulties of establishing the etiology of pneumonia, these isolates could prove useful in determining patterns of antimicrobial susceptibility in a specific area, allowing the behavior of the serotypes responsible for invasive disease in the same area to be predicted (*19*).

The colonization rate documented in the present study is similar to rates reported in Uruguay (*20*) and in a community in the State of Virginia (U.S.A.) (*21*). In contrast, studies conducted in other countries have found a higher prevalence of colonization in children with pneumonia, for example, 51% in the Philippines and 98% in Pakistan (*11, 22*). In Papua New Guinea, colonization rates of 100% have been reported in 3-month-old infants (*23*). Although no previous study has reported colonization rates in Colombian children with pneumonia, one recent investigation found *S. pneumoniae* in 46% of children in a day-care center in Santafé de Bogotá (*24*). In that study, the proportion of pneumococcal carriers was highest among children under 2 years of age.

Isolates of *S. pneumoniae* resistant to penicillin and other antibiotics are becoming increasingly frequent. In Spain, Hungary, and South Africa, very high rates of penicillin resistance have been found in both colonizing and invasive isolates (*9, 25*). The 17% frequency of diminished sensitivity to penicillin documented in this study is significantly higher than rates reported in Uruguay (3%) (*20*), Pakistan (12%) (*11*), and South Africa (12%) (*26*).

Serotypes 6, 14, 19, and 23 have been associated with resistance to penicillin or multiple drugs. These serotypes represent 60% of isolates found in children under 2 years old (*5, 21*). A clone of serotype 23F with resistance to penicillin and other antibiotics was first discovered in Spain; later, it was found in South Africa and the United States (*27, 28*). In the present study, 68% of

isolates resistant to penicillin belonged to serotype 23F. In Mexico, serotype 23F has also been found to be common among multiresistant isolates, accounting for 27% (*29*).

Marked differences have been recorded between the colonization rates and serotypes of *S. pneumoniae* isolates in healthy children compared to children with pneumonia. In Uruguay, healthy children were found to have a 15% colonization rate, while children with pneumonia had a 42% rate (*20*). In another study, isolates from healthy carriers were more frequently resistant than invasive isolates (*29*). The 17% rate of resistance to penicillin in nasopharyngeal isolates reported in the present study is higher than the 12% rate observed in invasive pneumococcal isolates analyzed using the Colombian National Serotyping Protocol (*Protocolo Nacional de Serotipificación*) for *S. pneumoniae* (unpublished data). However, this difference could be artifactual, since blood cultures—the technique used in the National Protocol—are much less sensitive than cultures of nasopharyngeal secretions (*1, 3*). Very likely, the resistance rate in the nasopharyngeal isolates is the better indicator of the behavior of circulating *S. pneumoniae*.

Noteworthy among the results of this study is the high percentage (40%) of colonizing *S. pneumoniae* with diminished susceptibility to co-trimoxazole; a substantial proportion (22%) showed complete resistance and, frequently, simultaneous resistance to co-trimoxazole and penicillin. In the past 15 years, resistance rates of *S. pneumoniae* to co-trimoxazole have been found to range from 18% to 40% in various countries (*20, 25, 30, 31*). This level of resistance necessitates a reconsideration of the WHO recommendation, in its ARI guidelines, that this agent be used as the treatment of choice for pneumonia.

Few isolates in this study exhibited resistance to erythromycin or chloramphenicol. Therefore, resistance to these two agents seems not to be a problem in Colombia at present. In this respect the Colombian situation resembles those of the United States and Australia, where pneumococcal resistance to macrolides is low (*32, 33*), and it contrasts with those of France, where such resistance reaches 29% (*34*), and Spain, where 30% resistance to chloramphenicol has been found (*35*). In Colombia, erythromycin and chloramphenicol are probably the treatments of choice in childhood pneumonia.

Among the factors associated with harboring or becoming infected with resistant strains of *S. pneumoniae* is a history of antimicrobial use (*26, 36*). In South Africa, for example, individuals who received penicillin and chloramphenicol were significantly more likely to carry strains resistant to these antibiotics (*30*). In this study, prior antibiotic use was significantly associated with the presence of resistant *S. pneumoniae*. β-lactam antibiotics were found to be administered most commonly. These data agree with other reports in the literature (*26, 30*).

In summary, the data from this study are consistent with findings reported in other published works and indicate important associations between age, prior use of antibiotics, and colonization by *S. pneumoniae* with diminished antimicrobial sensitivity. An association between nasopharyngeal carriage of resistant pneumococcal isolates and the diagnosis of severe pneumonia was also indicated, but the size of the sample was not very large and the association was not statistically significant in all cases.

The performance of similar studies in other regions of Colombia would clarify the scope of the problem posed by *S. pneumoniae* resistance to antibiotics, provide a basis for a true program of surveillance of pneumococcal resistance, and guide the rational use of common antimicrobial agents against this important pathogen.

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Susceptibilidad antimicrobiana de *Streptococcus pneumoniae* colonizante de nasofaringe en niños colombianos con neumonía

RESUMEN

Streptococcus pneumoniae es uno de los principales agentes causales de infección respiratoria aguda (IRA) en niños y su resistencia a antibióticos se ha incrementado en todo el mundo. En este estudio se determinaron los patrones de susceptibilidad a antimicrobianos de *S. pneumoniae* colonizante de las vías respiratorias altas en 272 niños hospitalizados por neumonía en dos hospitales de Santafé de Bogotá. Se aisló *S. pneumoniae* en 114 pacientes (42%). Se observó susceptibilidad disminuida a la penicilina en 19 aislamientos (17%), con sensibilidad intermedia en 12 (11%) y franca resistencia en 7 (6%). Solo 1 de los 19 aislamientos resistentes a penicilina mostró también resistencia a la ceftriaxona. Se observó sensibilidad disminuida a la eritromicina en 3 aislamientos (3%), al cloranfenicol en 6 (5%) y al cotrimoxazol (trimetoprima + sulfametoxazol) en 46 (40%). Se encontró multirresistencia en 7 aislamientos (6%). El serotipo con sensibilidad disminuida a la penicilina que se halló con mayor frecuencia fue el 23F (68.4%). Se observó una asociación entre la edad, el uso previo de antibióticos y la colonización con *S. pneumoniae* con susceptibilidad disminuida a la penicilina o multirresistencia. Este estudio confirma la presencia de resistencia antimicrobiana de *S. pneumoniae* en Colombia y resalta la importancia del uso racional de los antibióticos y de la implementación de la vigilancia epidemiológica sobre este agente.

PETROQUIM' 98–Coloquio Iberoamericano de Seguridad Integral, Salud Ocupacional y Medio Ambiente para la Industria Petrolera y Química

Fechas: 28 a 30 de mayo de 1998
Lugar: Hotel Calypsso, Balneario de Salinas, Ecuador
Temas: Intercambio de avances en materia de prevención de riesgos ocupacionales y ambientales

El Coloquio, apoyado por la Comisión Técnica Permanente de Riesgos Profesionales de la Organización Iberoamericana de Seguridad Social y difundido por la Sociedad Ecuatoriana de Seguridad Profesional (SESO) y la Asociación Chilena de Seguridad (ACHS), está dirigido a los profesionales y encargados de la seguridad e higiene laboral, salud ocupacional y medio ambiente en la industria petrolera y química de todos los países hispanoparlantes. Entre los temas centrales figuran los de auditorías medioambientales, responsabilidad integral y ecoeficiencia, herramientas informáticas para la evaluación de riesgos, epidemiología de las enfermedades ocupacionales y programas de emergencias, todo ello en relación con la industria química y el sector petrolero.

El costo por participante es de US$ 450 cuando los asistentes de una misma empresa son menos de cuatro; de US$ 400 cuando son más de cuatro; o de US$ 350 cuando son más de siete. La forma de pago es por cheque certificado a nombre de SESO y pagadero en cualquier banco de los Estados Unidos de América, o bien por transferencia bancaria a la cuenta de SESO no. 164060620 del Pacific National Bank de Miami, EUA.

Información:
Secretaría Oficial de Petroquim' 98
Sociedad Ecuatoriana de Seguridad y Salud Ocupacional (SESO)
Chambers 105 y Amarilis Fuentes (esquina)
Casilla (POB) 7015
Guayaquil, Ecuador
Teléfono: (593-4) 330 706
Fax: (593-4) 580 189