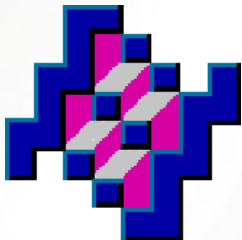




Epidemiology and Surveillance of Pneumococcal Disease

Antibiotic resistance in Latin America



Gabriela Echániz-Aviles, Ph.D.
Instituto Nacional de Salud Pública, México
SIREVA II Group

Content

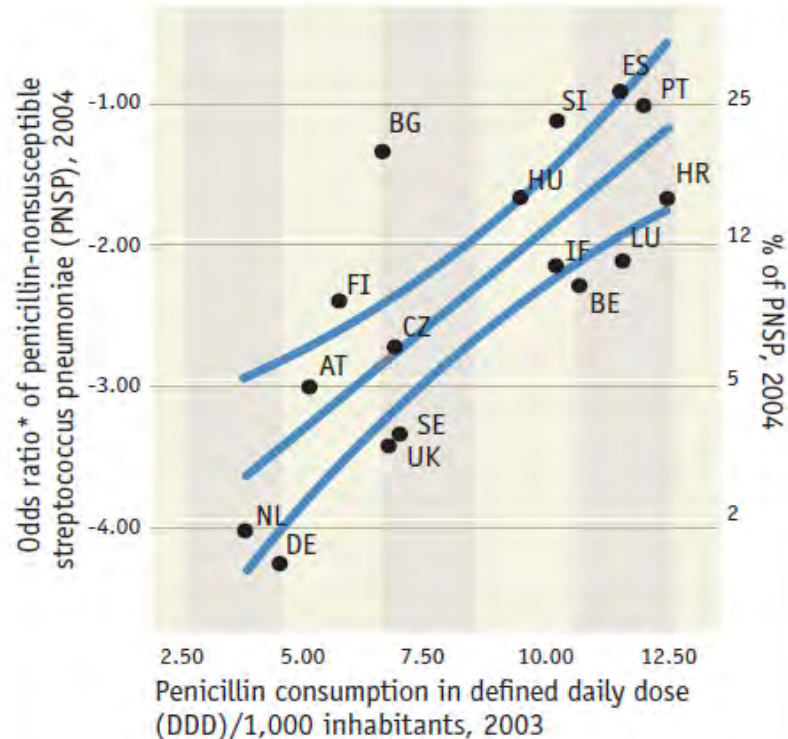
1. Antibiotic consume in Latin America
2. SIREVA network
3. Pneumococcal antimicrobial susceptibilities
4. Multiresistant clones
5. Conclusions

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Antimicrobial consumption and Spn resistance

Occurrence of Spn against outpatient use of penicillins in 17 European countries



*On a log scale

AT Austria, BE Belgium, BG Bulgaria, CZ Czech Republic, ES Spain, FI Finland, GR Greece, HR Croatia, HU Hungary, IE Ireland, LU Luxembourg, NL Netherlands, PT Portugal, S Sweden, SI Slovenia, UK United Kingdom

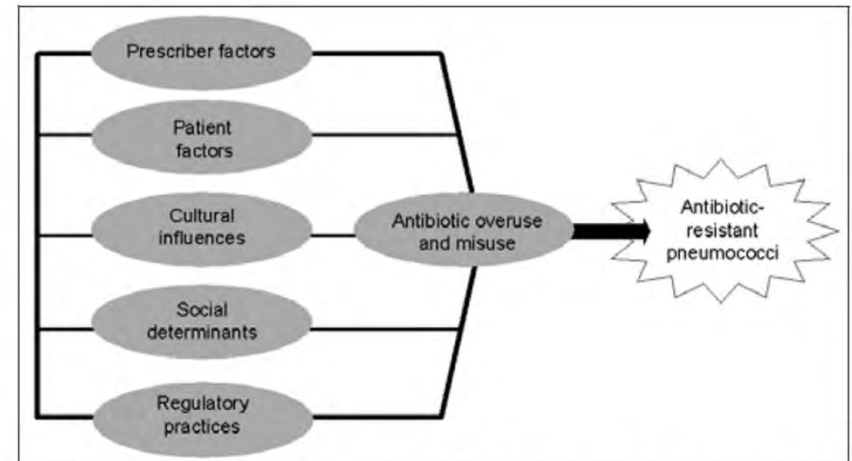


Figure 2. Framework of nonmicrobiologic factors influencing outpatient antibiotic use and prevalence of pneumococcal resistance.

Harbarth S. et al. Emerg Infect Dis 2002; 1460-67

van de Sande-Bruinsma N et al. Emerg Infect Dis 2008; 14:1722-30

Antimicrobials in Latin America

Common problems:

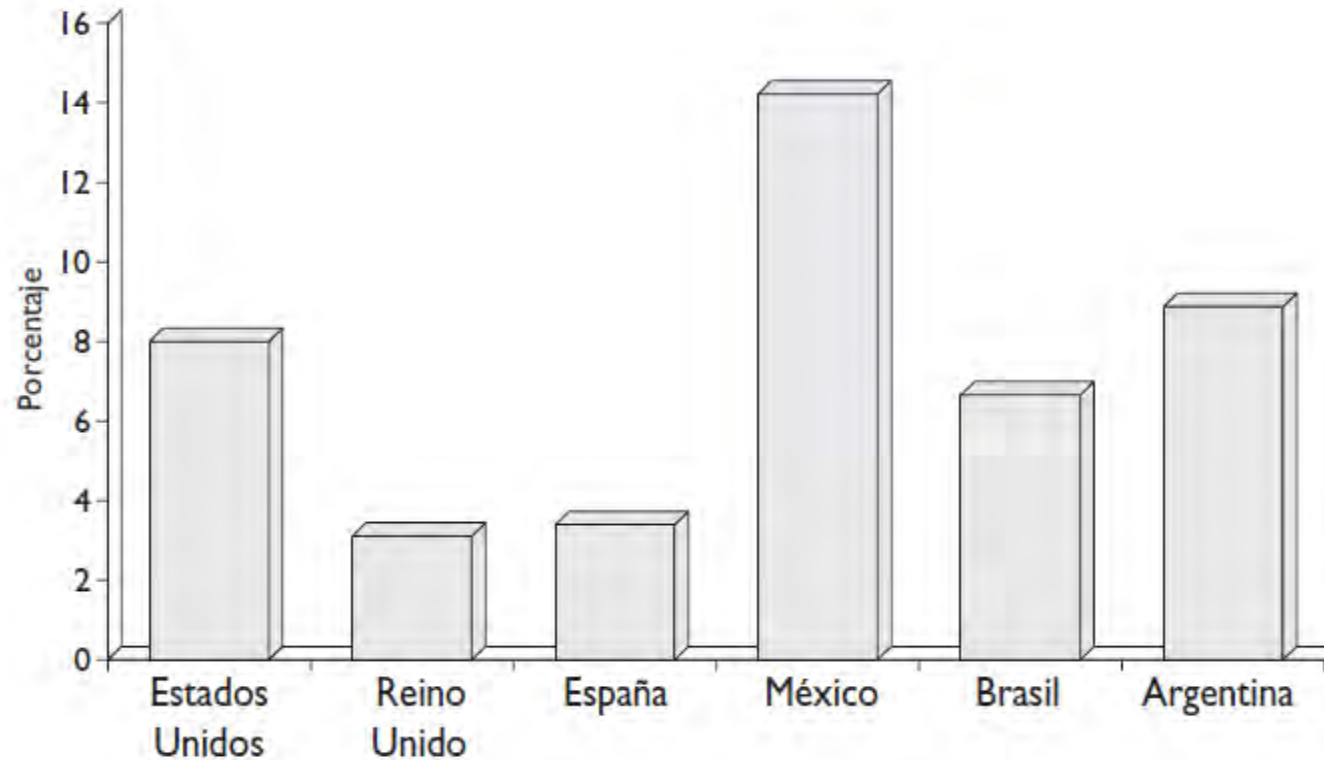
- High incidence of infectious diseases
- Great number of pharmaceutical products available
- Lack of stringent policies regarding medicine commercialisation
- Frequent self-medication
- Lack of independent information on medicines
- Lack of knowledge regarding local antimicrobial susceptibility patterns



Misuse of antibiotics

Wolff, *Clin Infect Dis* 1993; Guzmán-Blanco, *Infect Dis Clin North Am* 2000;
Castanheira, *Clin Microbiol Infect* 2004; Sosa y Travers, APUA-PAHO Report 2002

Sales percentage of antimicrobials within the Annual Medicine Market



Fuente: IMS-Health 2005

Trends in antibiotic utilization in 8 LA countries

- 8 countries: Argentina, Brazil, Chile, Colombia, Mexico, Peru, Uruguay and Venezuela
- Oral and injectable antibiotics (Codes J01 ATC), total and by groups
- Converted to daily doses defined by 1,000 inhabitants per day (**DHD**)
- 10 years (1997 – 2007)

Wirtz et al, *RevPanamSaludPublica* 2010

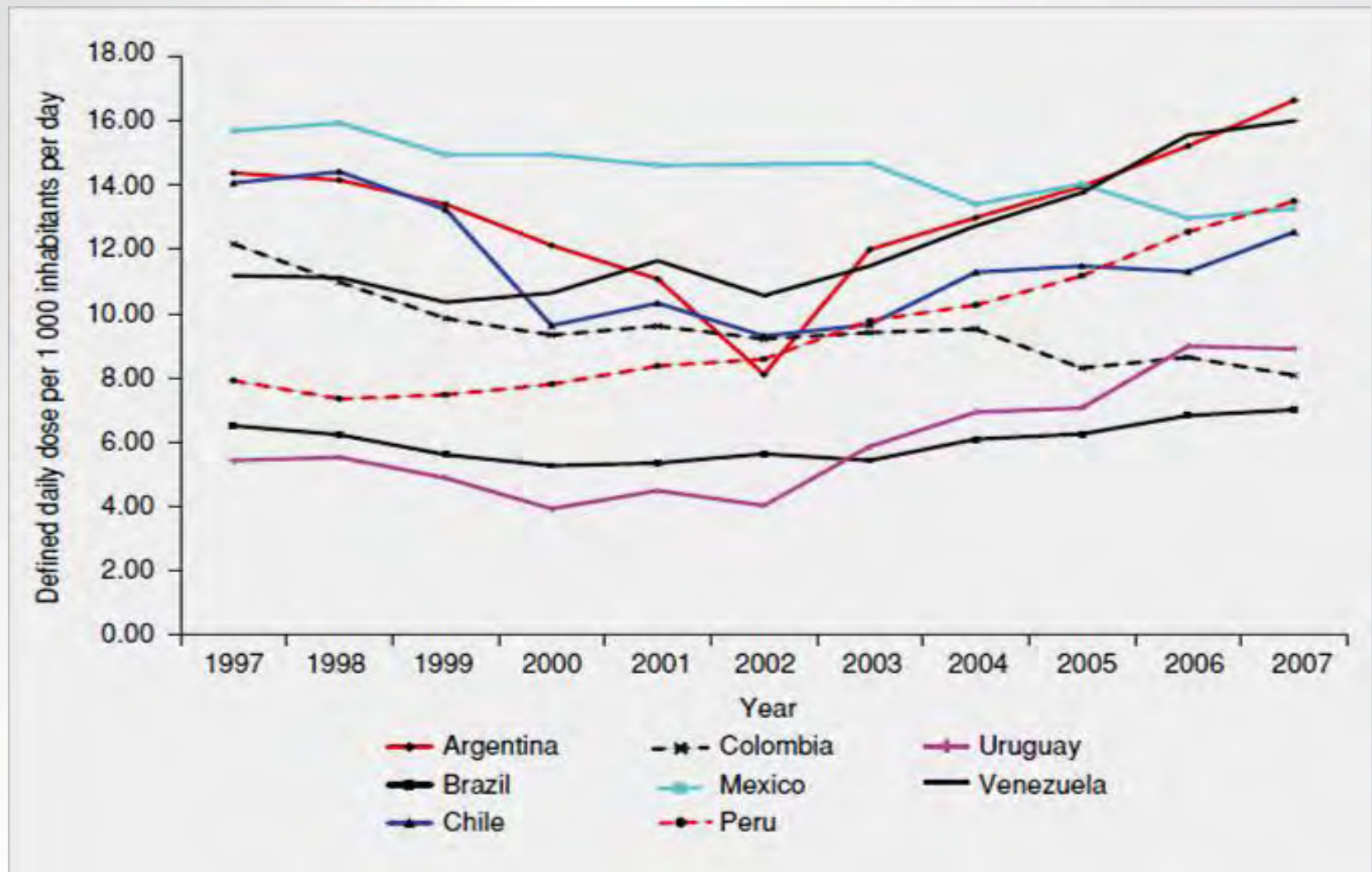
Investigación original / Original research

Trends in antibiotic utilization in eight Latin American countries, 1997–2007

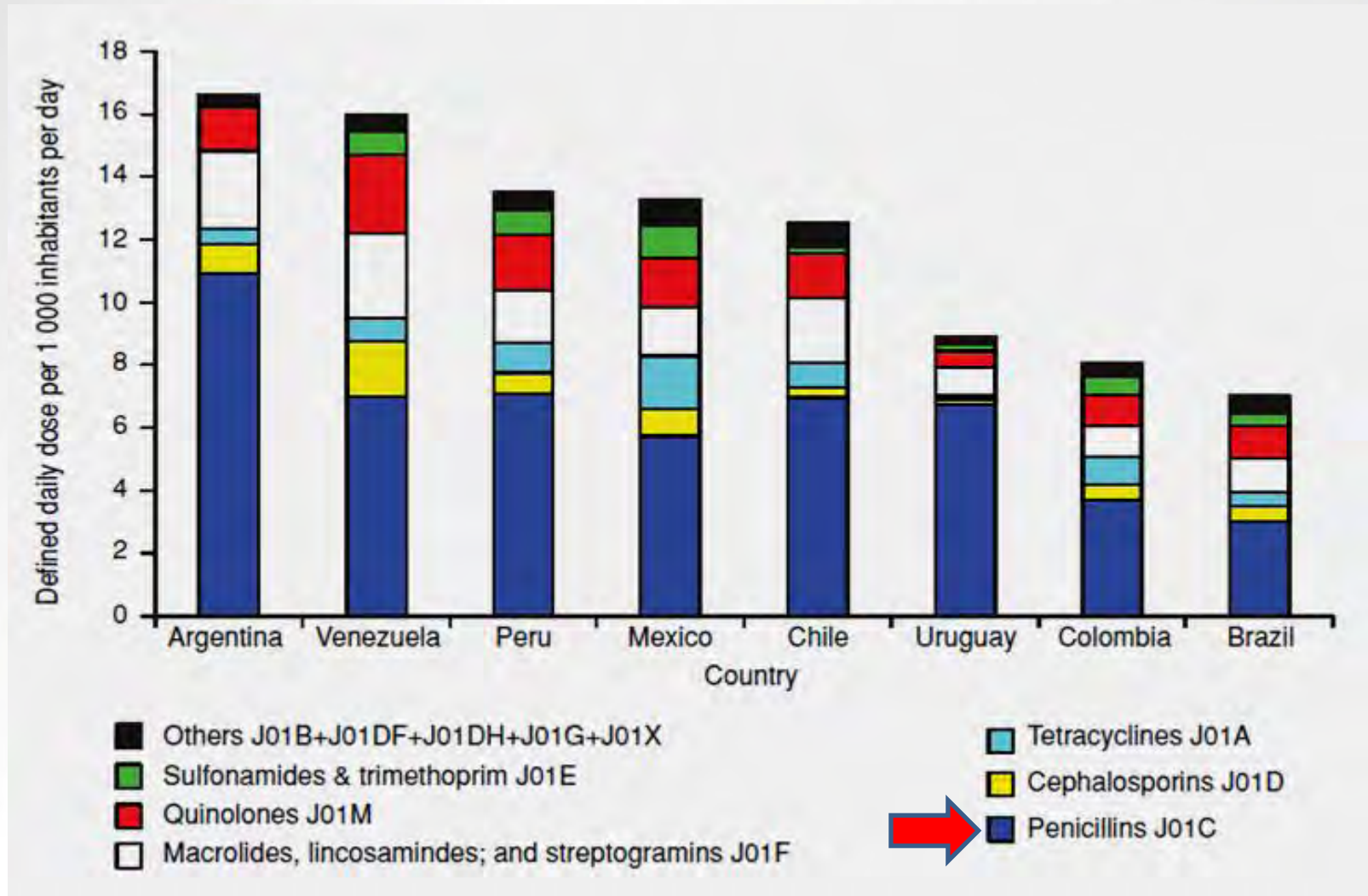
Veronika J. Wirtz,¹ Anahí Dreser,¹ and Ralph Gonzales²



Consumption of antibiotics in Latin America

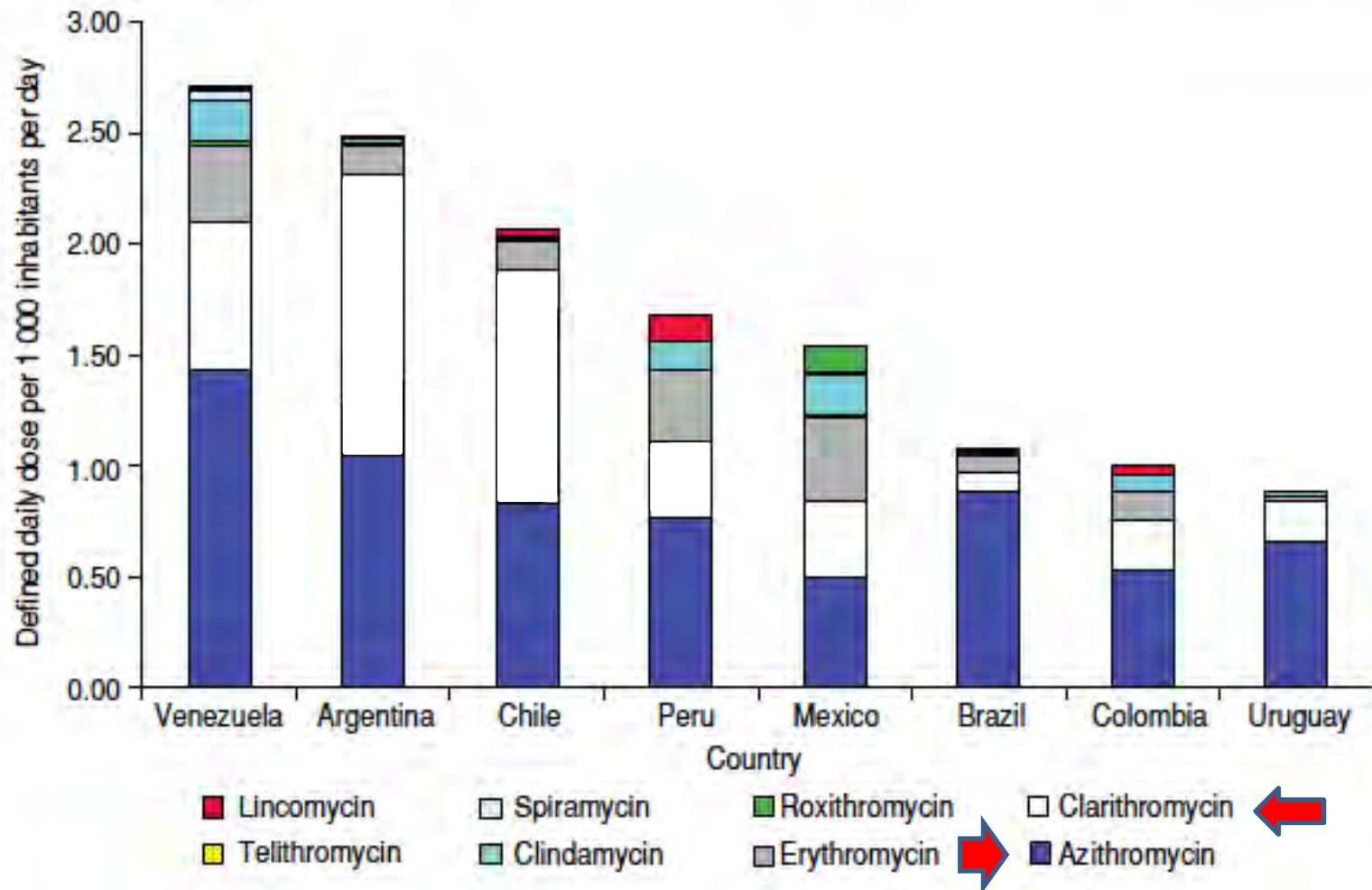


Consumption of antibiotics in Latin America : therapeutic class (2007)



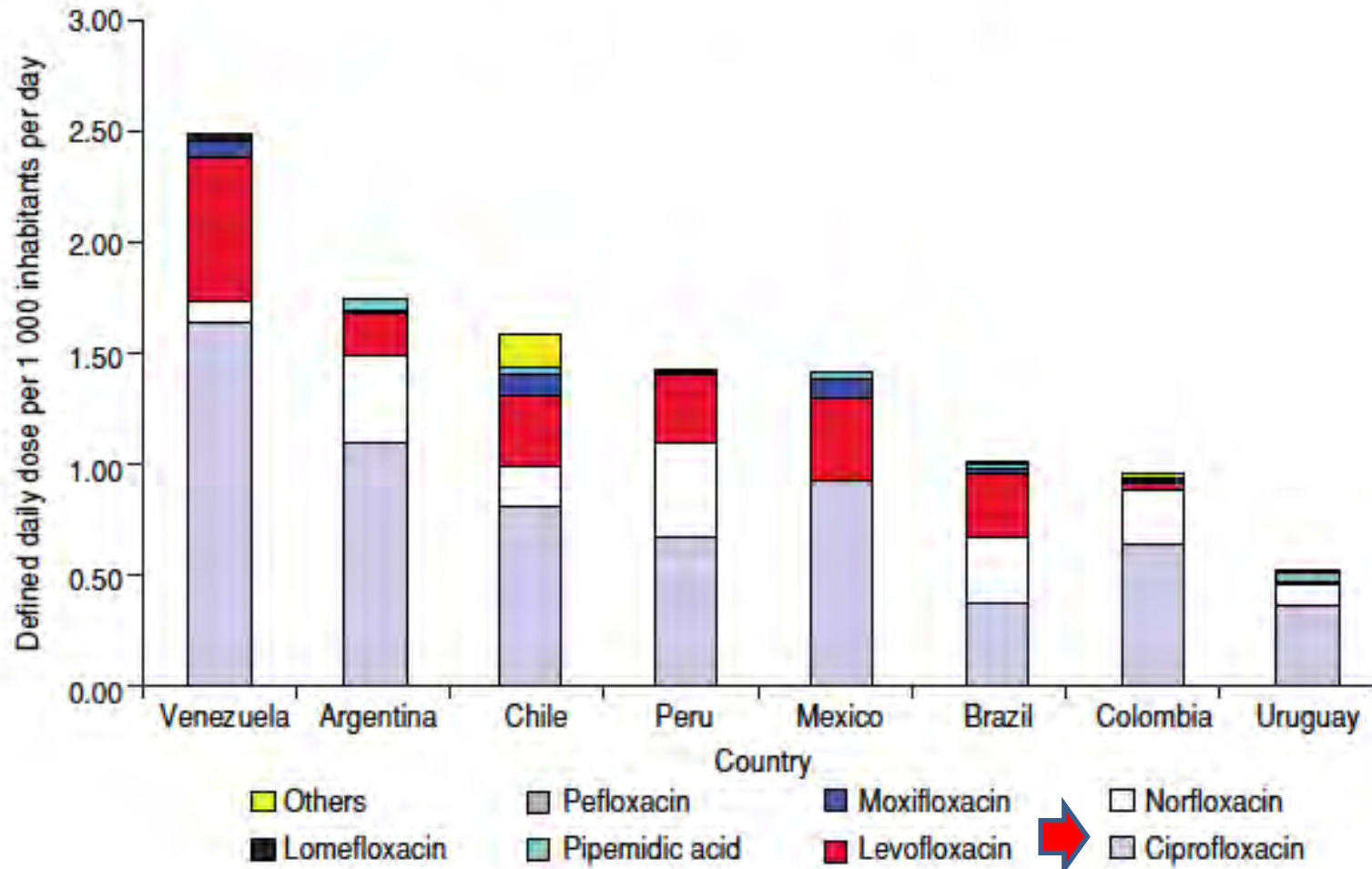
Macrolides, lincosamides and streptogramins

FIGURE 4. Utilization of macrolides, lincosamides, and streptogramins in eight Latin American countries, 2007



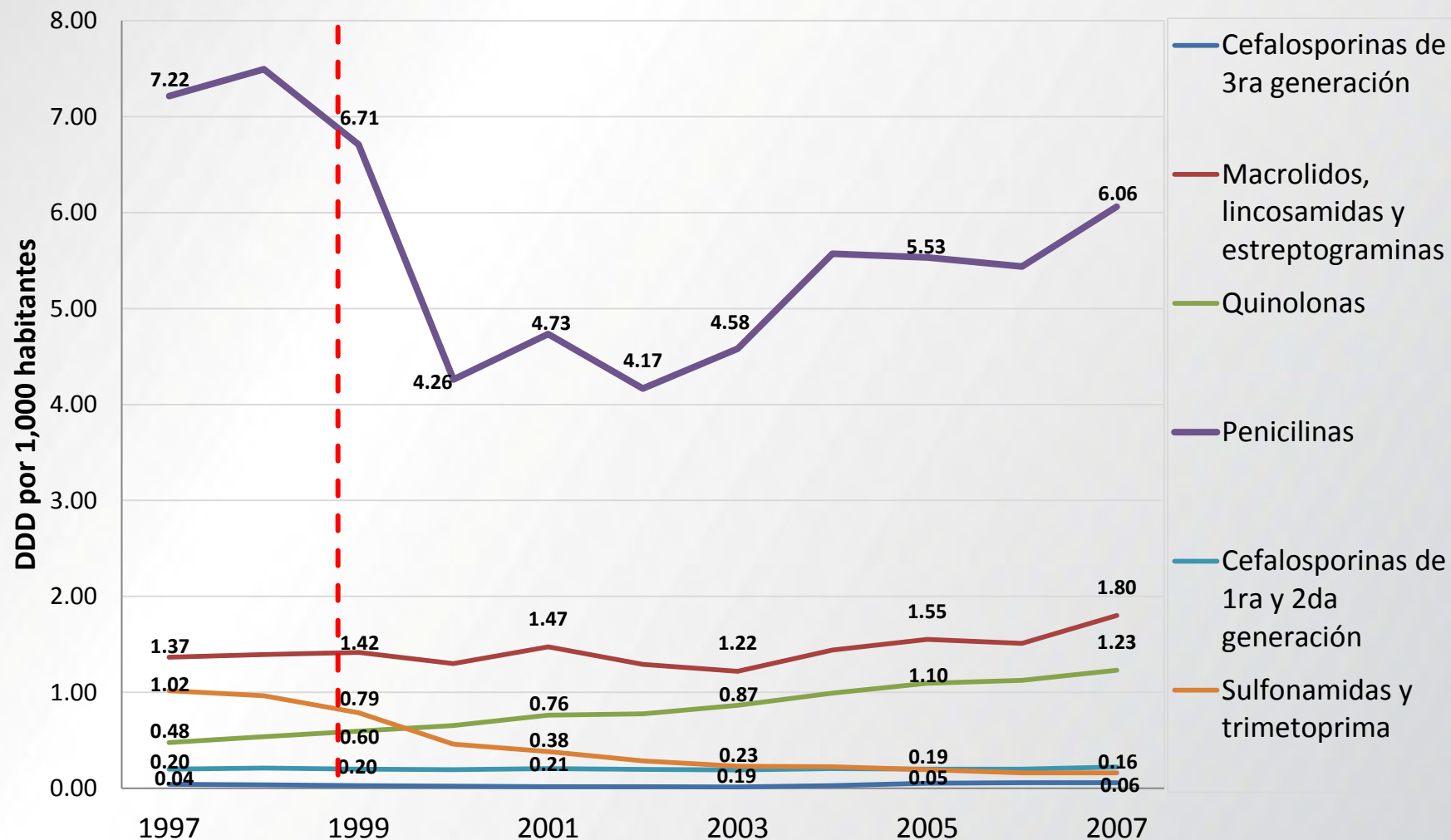
Quinolones

FIGURE 6. Quinolone utilization in eight Latin American countries, 2007





Optimize antibiotic use: The case of Chile



Wirtz et al. Impacto de la regulación de venta de antibióticos con receta médica en Chile y Venezuela. 14 Congreso de Investigación en Salud Pública, 2011.



Optimize antibiotic use: The case of Mexico

➤ Influenza epidemic opened an opportunity to consolidate the national strategy of antimicrobial control

Propondrá SSA venta de antibióticos sólo con receta

El Universal, 17/10/2009



México.- El secretario de Salud, José Ángel Córdova, anunció un proceso para que la venta de antibióticos con función de automedicación **haga sólo con receta, a fin de controlar la automedicación.**

Subrayó que la costumbre de automedicarse cuando se presentan síntomas de resfriado o enfermedades respiratorias provoca que el paciente no consulte con un médico en forma oportuna, lo que en el caso de la influenza humana ha provocado la muerte de muchos mexicanos.



Optimize antibiotic use: The case of Mexico

Consultorios en farmacias:

- Incentivo económico perverso para venta de AB
- Riesgo de incrementar utilización de AB de amplio espectro

Necesidad de complementar la medida regulatoria con:

- Campañas educativas para la población
- Vigilancia de calidad de prescripción
- Análisis del impacto en gasto y tendencias de consumo de AB



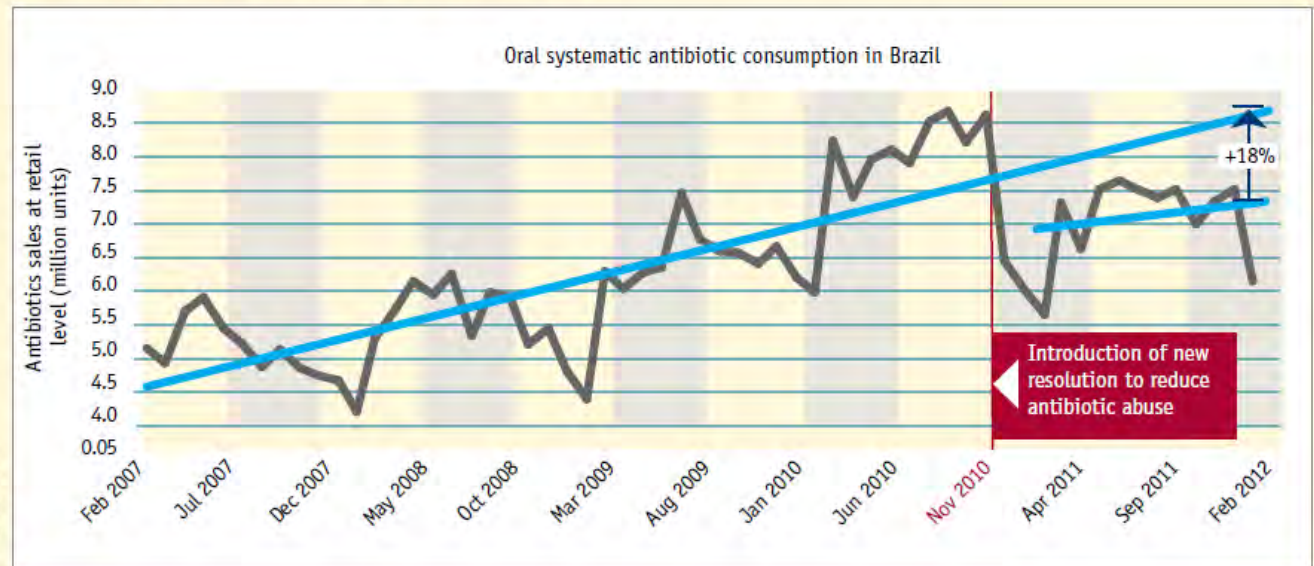
Optimize antibiotic use: – Brazil



OUTCOMES

- Estimates of antibiotic consumption at the retail level are reduced 18% today compared to without legislation.
- This supports the aim of controlling patients' antibiotic use.

AN ANTIBIOTIC FORECAST IN THE RETAIL SECTOR SHOWS THAT WITHOUT THE LEGISLATION, BRAZIL'S ANTIBIOTIC USE WOULD BE ABOUT 18% HIGHER



Sources: IMS,
Pharmaceutical Market
Brazil, Mar 2012; IMS
Institute for Healthcare
Informatics, 2012.

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SIREVA NETWORK

“Despite the importance of *S.pneumoniae* as a cause of invasive disease in the world, there are very few studies in the region that demonstrate its importance.

To respond to this necessity, the Pan-American Health Organization (PAHO), through the Vaccines and Immunizations (VI) special program and the regional vaccines system (SIREVA), and with financing from the Canadian International Development Agency (CIDA), started the epidemiological surveillance of *S. pneumoniae* in the region...”

Di Fabio JL, Homma A, de Quadros C. Microb Drug Resist. 1997; 3:131-3.

EQA program for *S. pneumoniae* - *H. influenzae*: SIREVA II network (1997-2012)

NLs: 20 countries

RRLs: Brazil and Colombia

IRLs: ISC III, Spain and CDC, USA



Global Invasive Bacterial Vaccine
Preventable Diseases countries
(IB-VPD) WHO



Country	1994-98	2000-05	2006-10	2011	total
Argentina	1.006	1.277	1.431	424	4.138
Bolivia		151	166	51	368
Brasil	1.203	4.169	4.128	921	10.421
CAREC		178	97	27	302
Chile	495	4.182	4.350	746	9.773
Colombia	623	1.396	1.598	400	4.017
Costa Rica		222	251	53	526
Cuba		1.283	215	74	1.572
Ecuador		60	255	57	372
El Salvador		88	183	41	312
Guatemala		247	70	25	342
Honduras		65	43	14	122
México	426	1.039	867	241	2.573
Nicaragua		55	50	10	115
Panamá		189	212	62	463
Paraguay		667	866	108	1.641
Perú		172	172	29	373
DominicanR		487	328	56	871
Uruguay	352	884	970	199	2.405
Venezuela		492	267	44	803
Total	4.105	17.303	16.519	3.582	41.509

No. Spn Isolates by Country
18-year period,
all age groups :
41,509
(SIREVA / SIREVA II)



 **IBVPD countries**

SIREVA

20 countries, 450 sentinel centers:

- *S. pneumoniae*: > 40,000 strains!!
- *H. influenzae*: > 2,782 strains
- *N. meningitidis*: > 6,908 strains

OPPORTUNITY!

<http://www.insp.mx/lineas-de-investigacion/medicamentos-en-salud-publica/enlaces.html>



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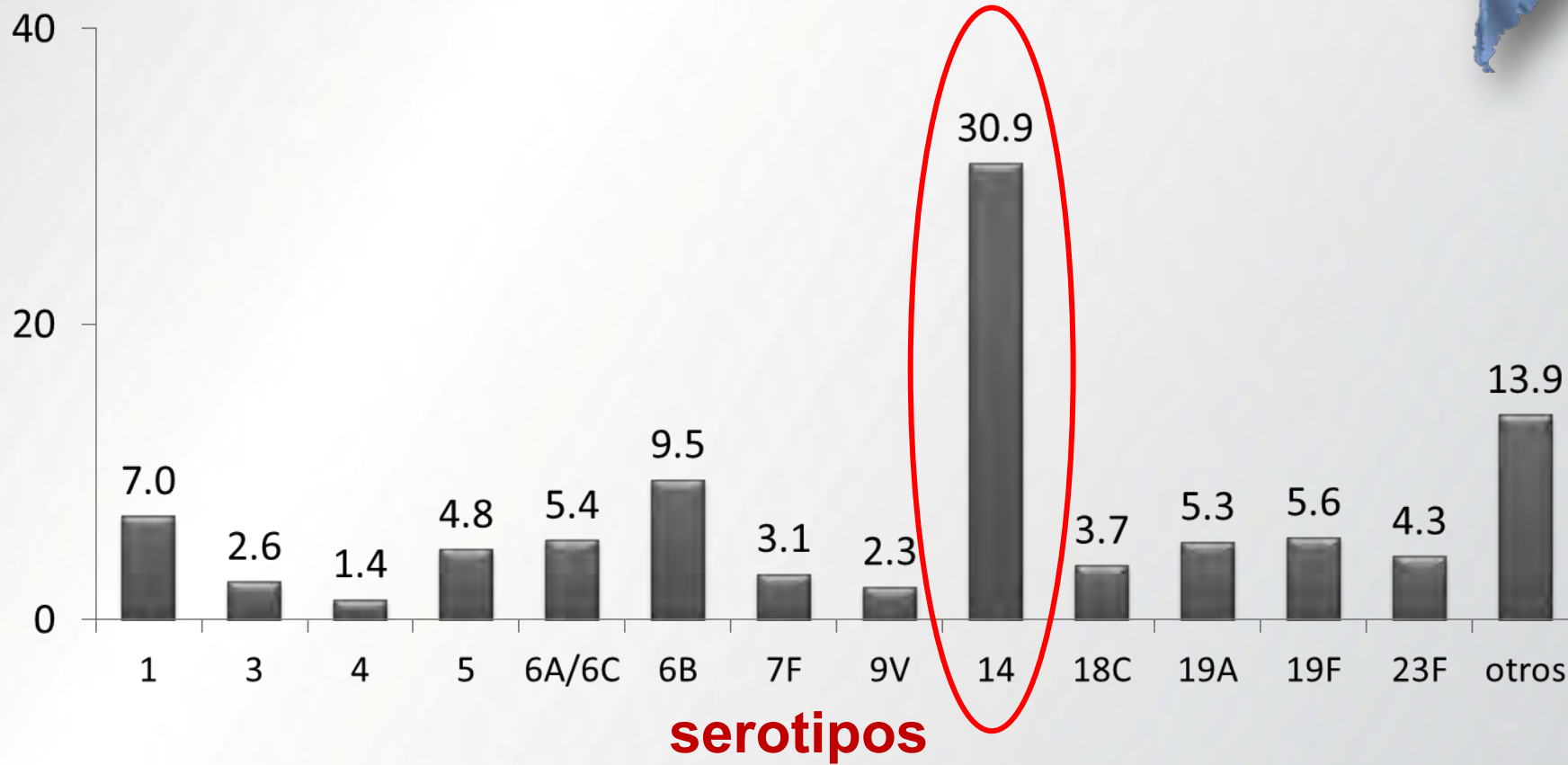
Introduction of Spn conjugate vaccine in the Region

Year	Country	Spn Vaccine
2008	Uruguay	PCV7 → PCV13
2008	Mexico	PCV7 → PCV10 → PCV13
2009	Peru	PCV7 → PCV13
2009	Costa Rica	PCV7 → PCV13
2010	Brazil	PCV10
2010	Colombia	PCV7 → PCV10
2010	Panama	PCV13
2010	El Salvador	PCV13
2010	Ecuador	PCV7 → PCV10
2011	Nicaragua	PCV13
2011	Honduras	PCV13
2011	Chile	PCV10
2012	Argentina	PCV13
2012	Paraguay	PCV10

Distribución de los serotipos vacunales de Spn, 2006-2010

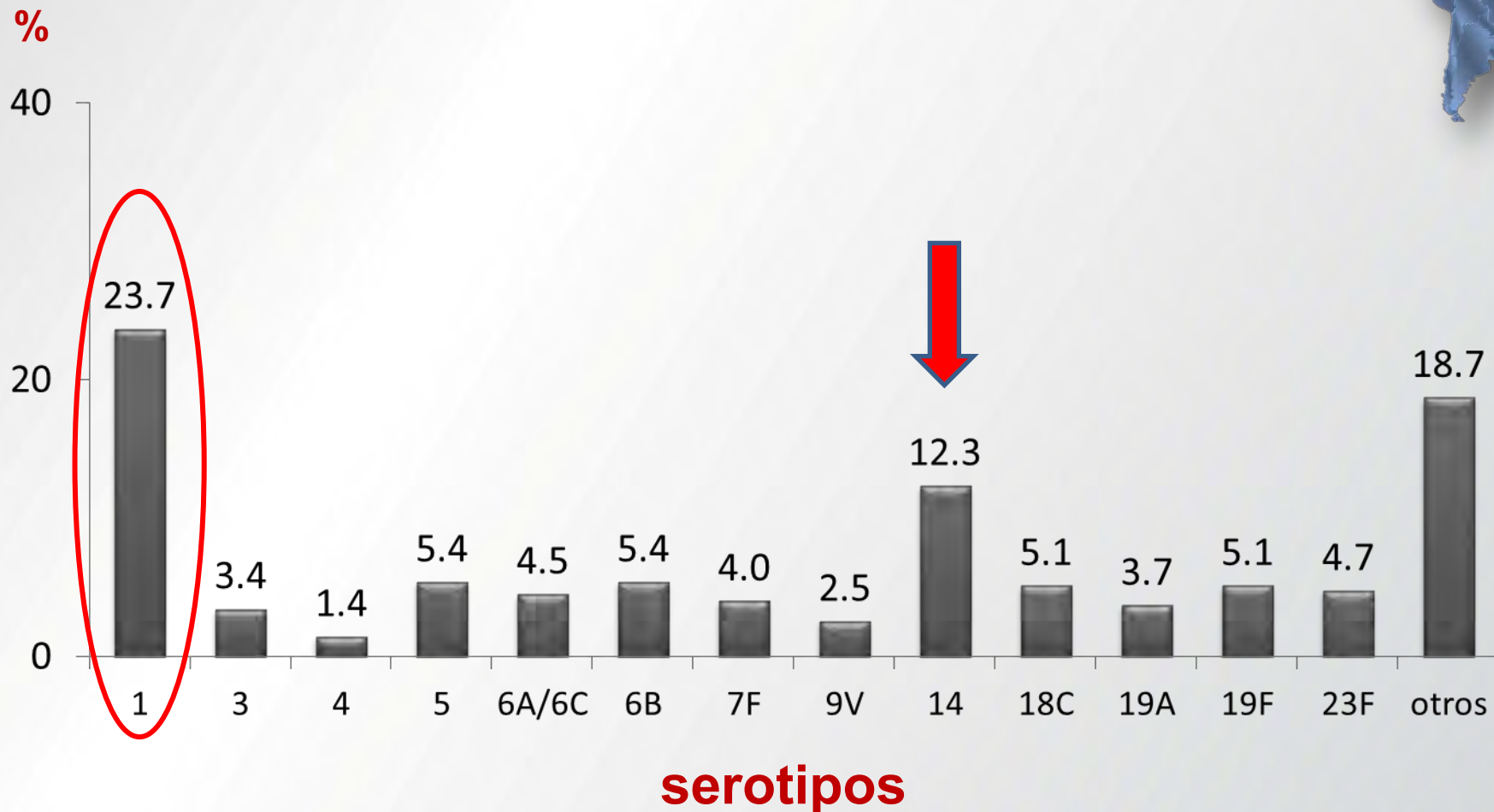
< 5 años n=6,949

%



Distribución de los serotipos vacunales de Spn, 2006-2010

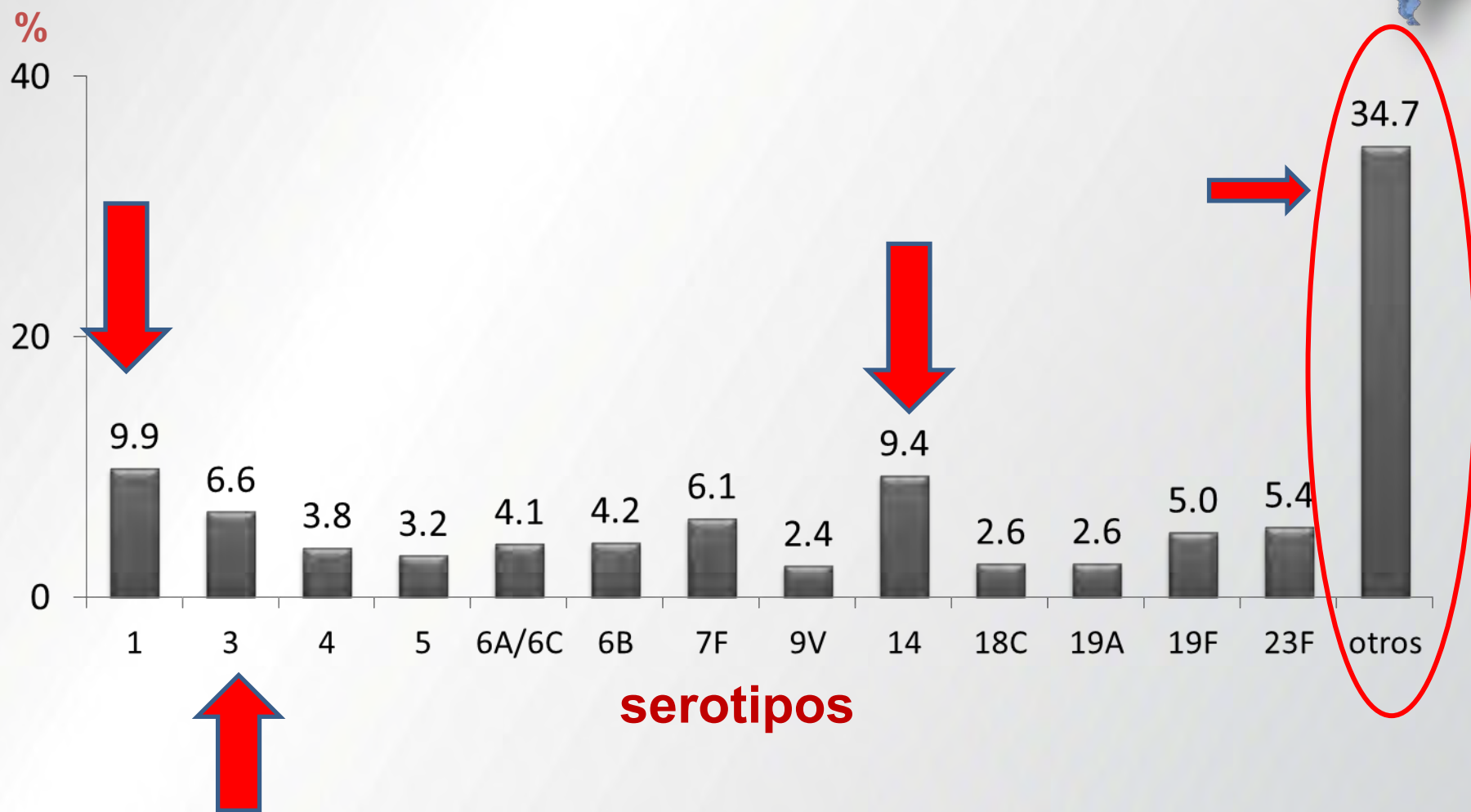
5 a 14 años n=1,898



Distribución de los serotipos vacunales de Spn, 2006-2010



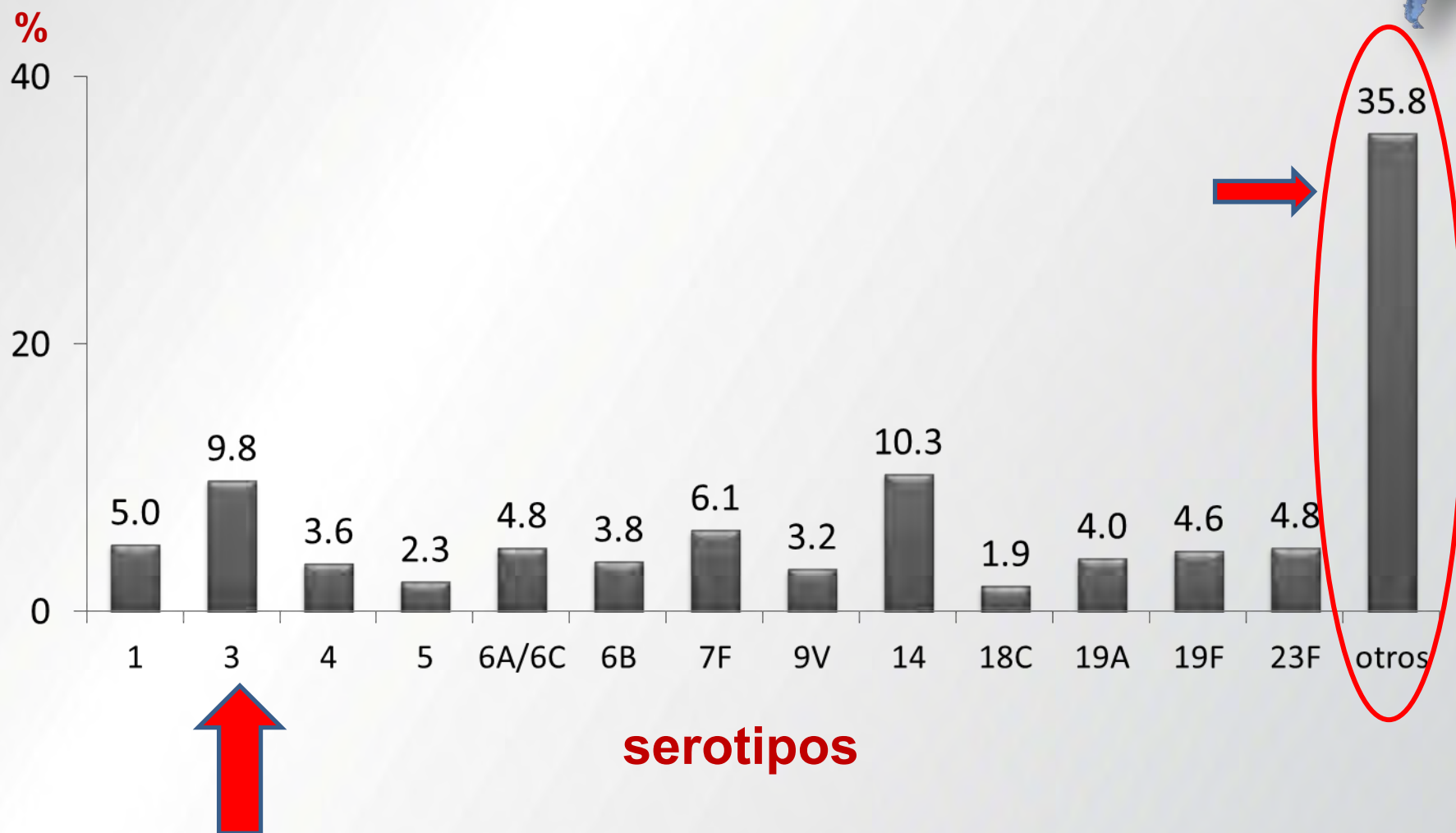
15 a 59 años, n=4,053



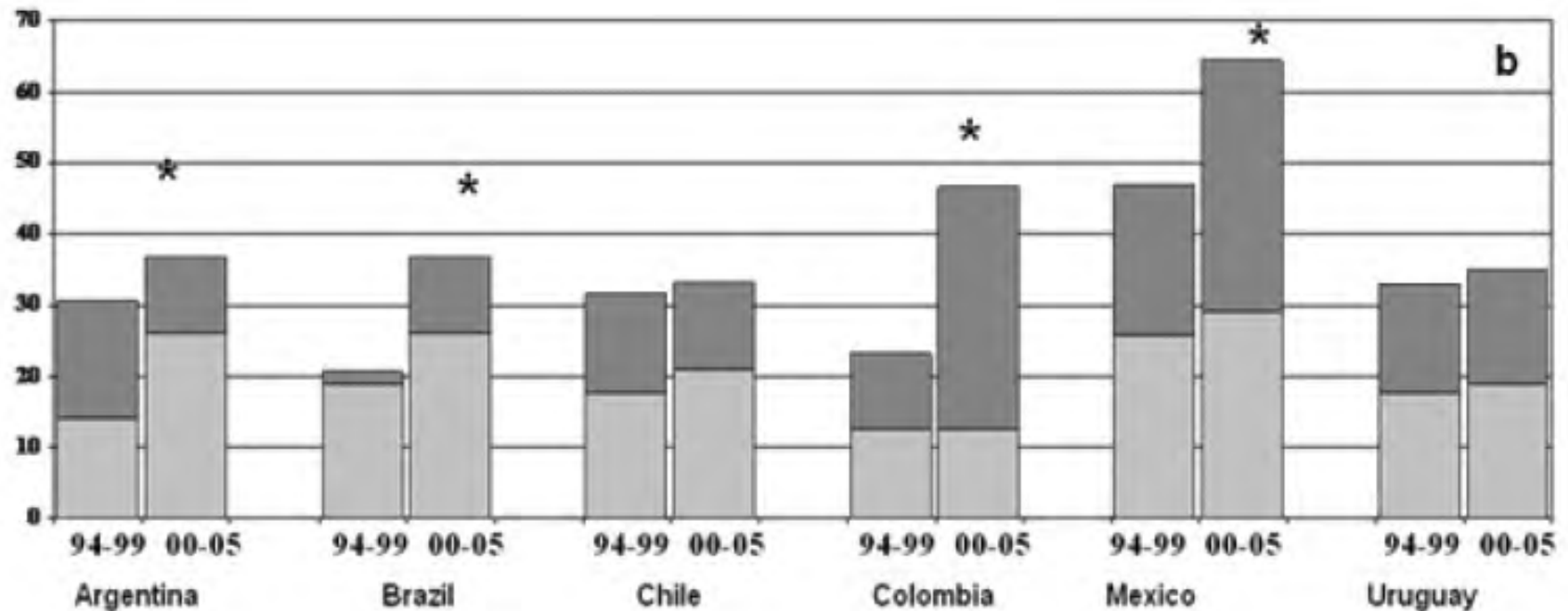
Distribución de los serotipos vacunales de Spn, 2006-2010



≥ 60 años, n= 1,626



Spn penicillin resistance in Latin America (94-99 vs 00-05)

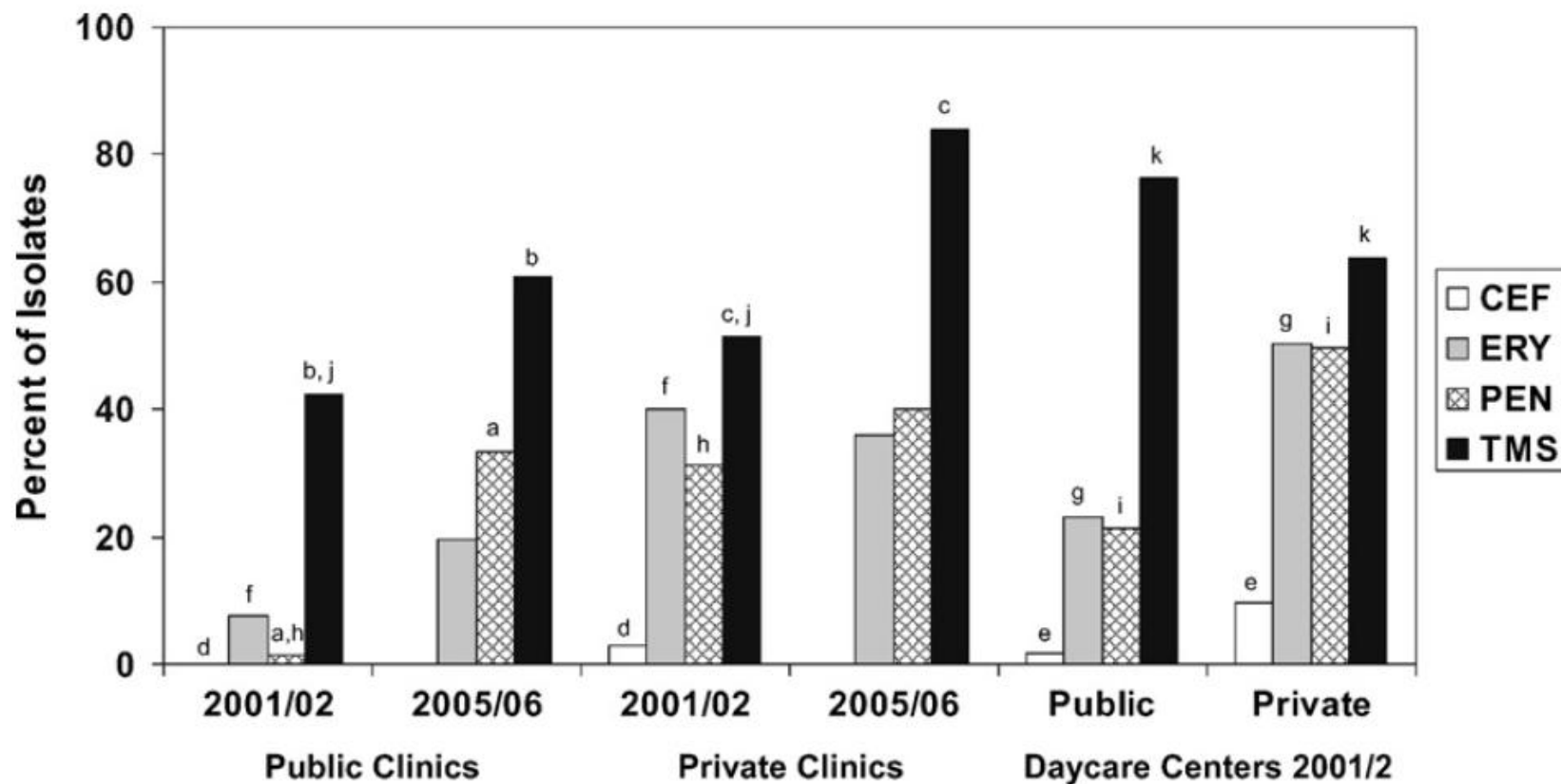


* $p < 0.001$

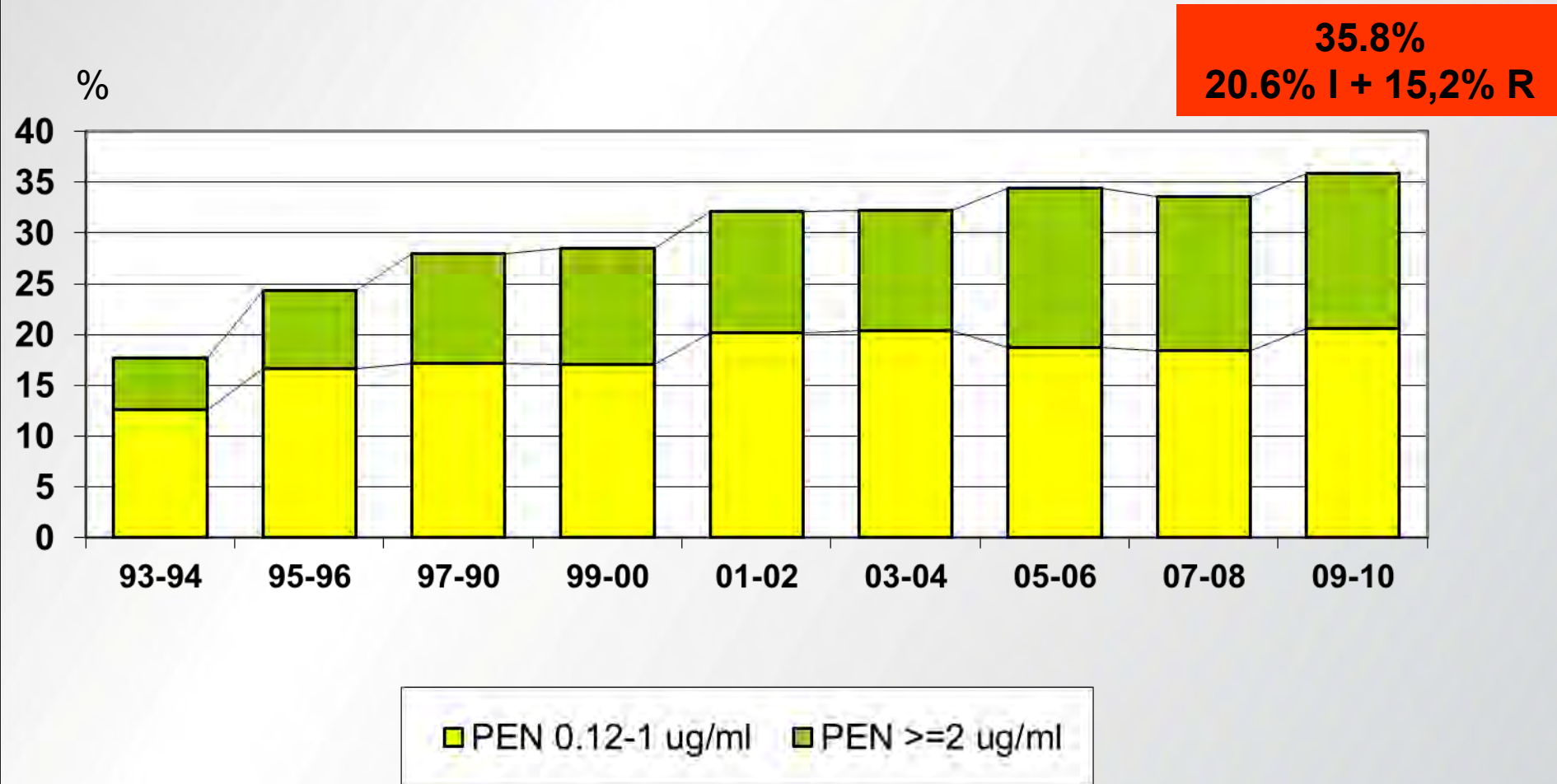
Figura 2. Tasas de resistencia del *Streptococcus pneumoniae* a la penicilina en Latinoamérica: incremento entre los periodos 1994-1999, y 2000-2005. Tomado de: Castañeda E, Agudelo CI, Regueira M, Corso A, Cunto-Brandileone MC, et al. Laboratory-Based surveillance of *Streptococcus pneumoniae* invasive disease in children in 10 Latin American Countries: A SIREVA II Project, 2000–2005. *Pediatr Infect Dis J* 2009; 28 (9): e265-e270.



Proportion of *S. pneumoniae* resistant isolates from children attending daycare centers and clinics in Guatemala



Evolution of Spn pencillin resistance in Latin America 1994-2010. < 6 years old

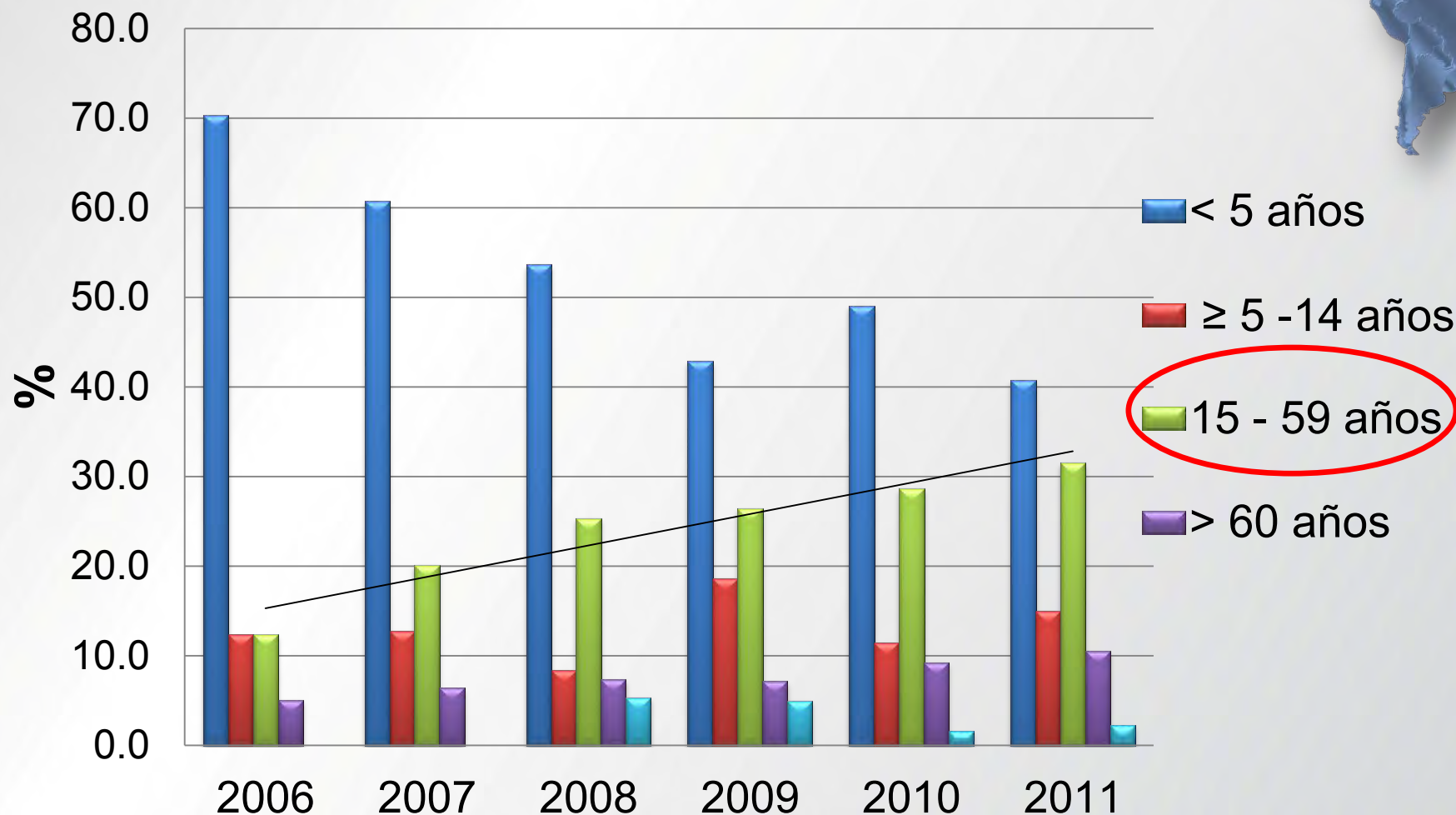


- PEN Resistance was around 35% over the last 5 years,
but increased in some countries: BRA, CHI, MEX, VEN, DR

Porcentaje de aislamientos de *Spn* resistentes a **penicilina** por grupos de edad: Meningitis

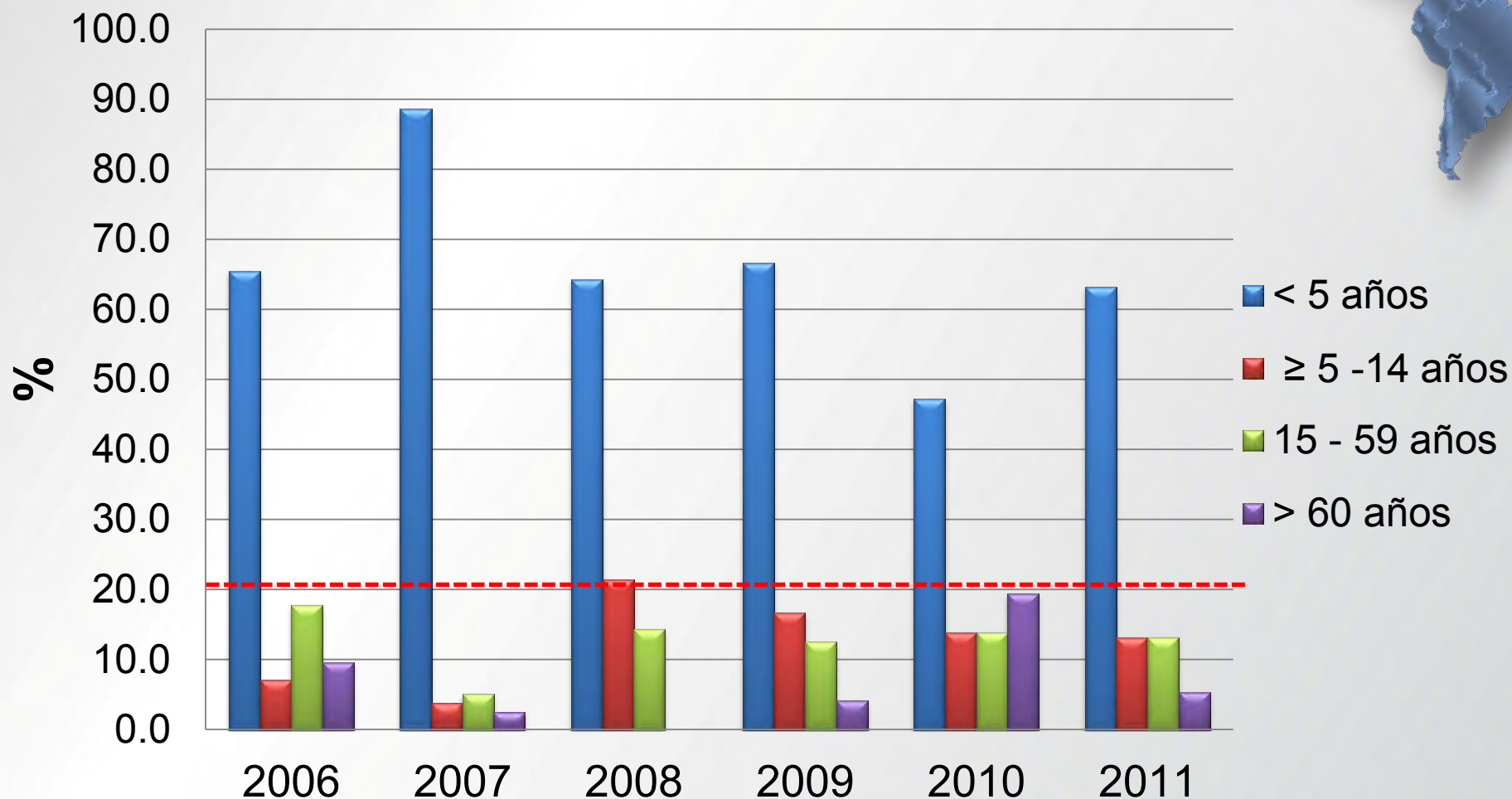


N=6,159

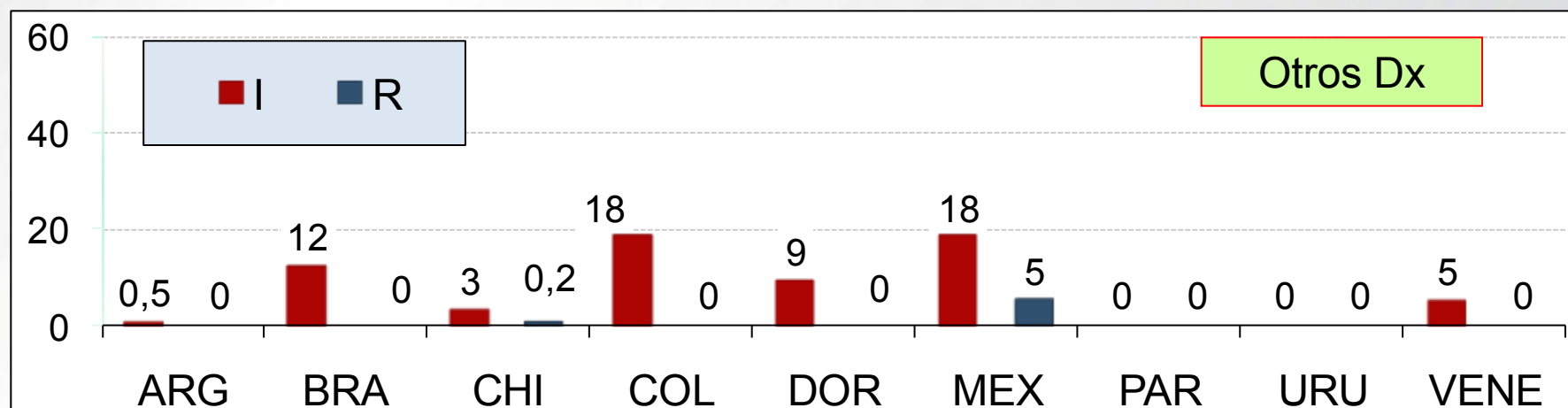
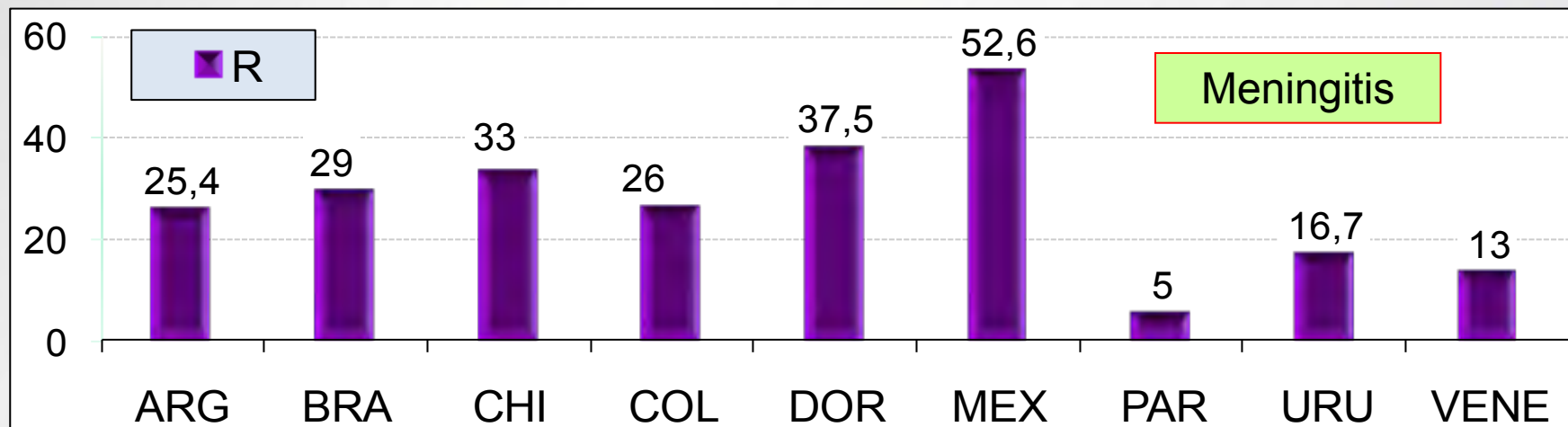


Porcentaje de aislamientos resistentes a **penicilina** por grupos de edad: **No meningitis**

N = 11, 591

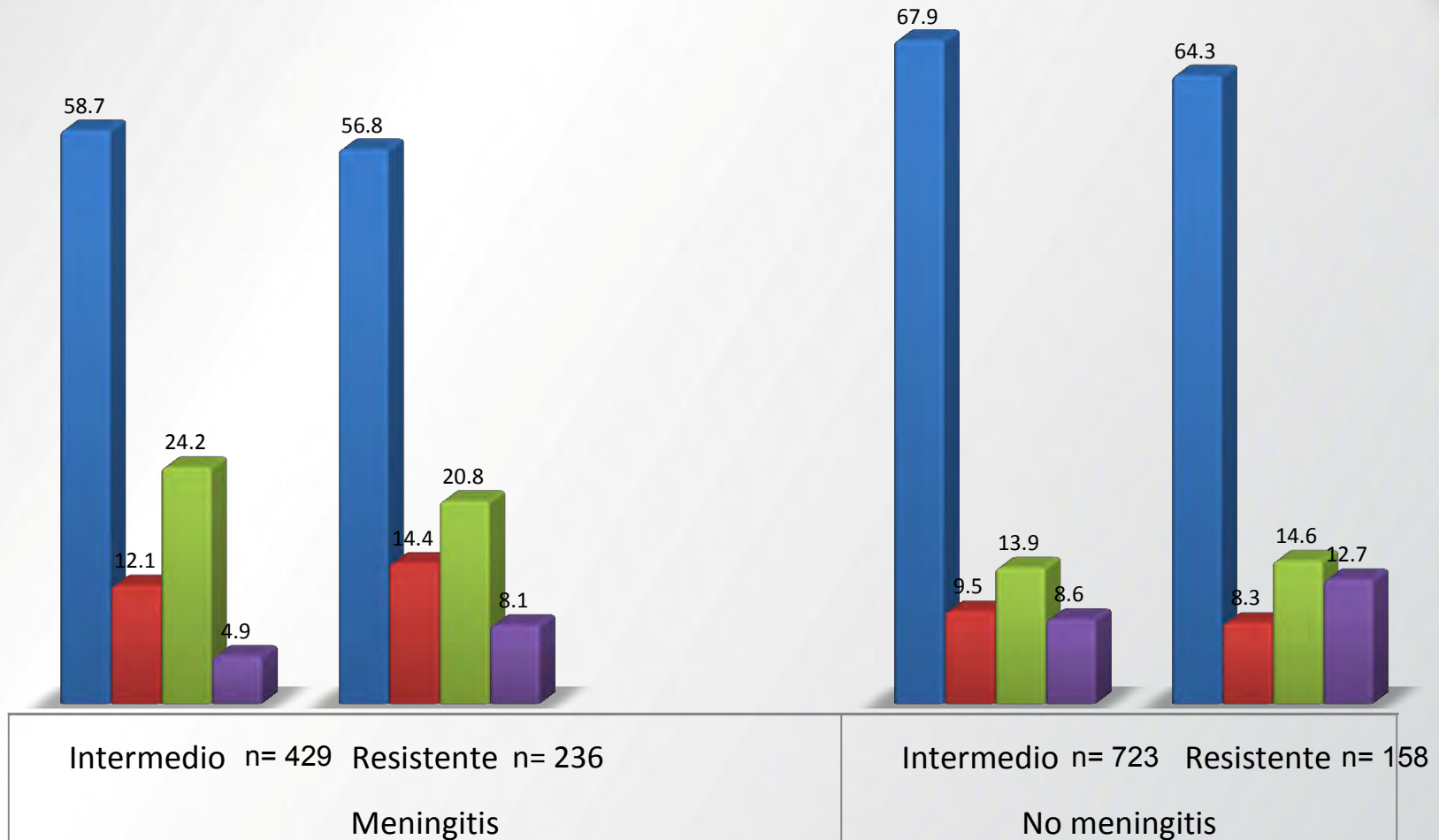


Resistencia a la **penicilina** de *S. pn.* aislados en 2009, criterios CLSI 2008

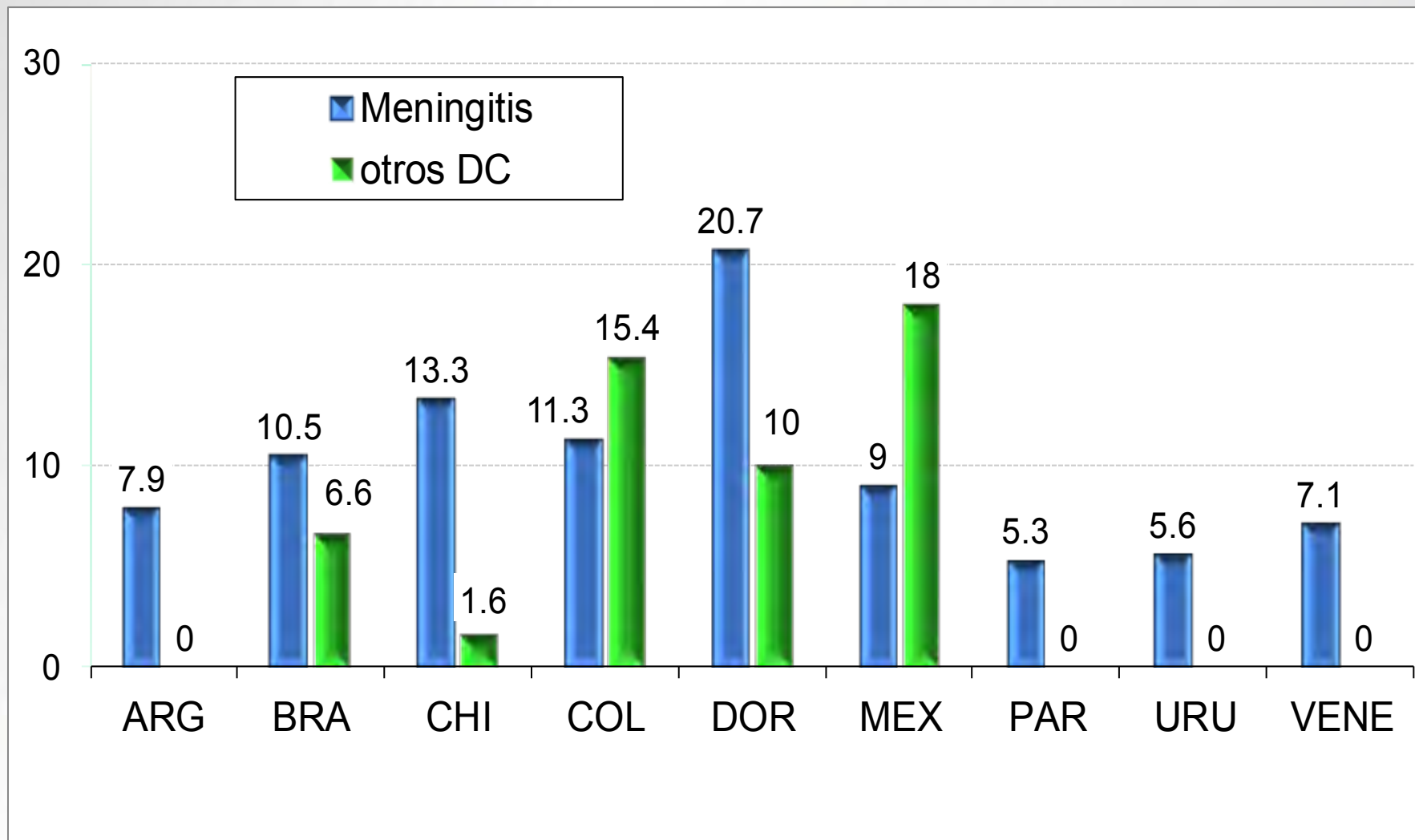


Resistencia a ceftriaxona por grupos de edad: 2006-2011. N= 18,208

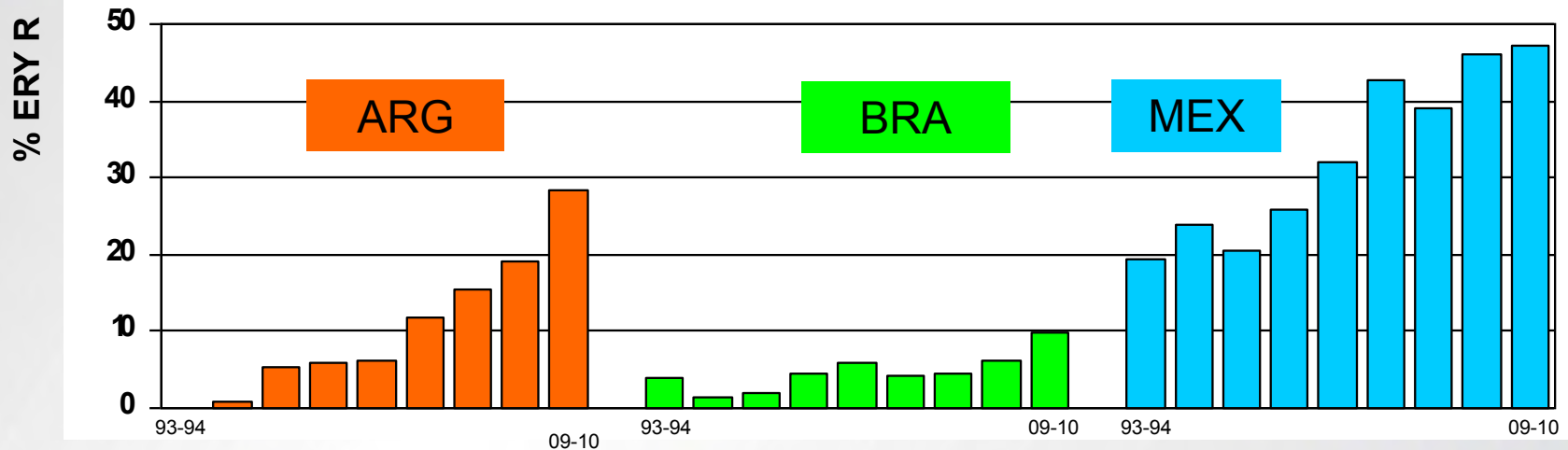
■ < 5 años ■ ≥ 5 -14 años ■ 15 - 59 años ■ > 60 años



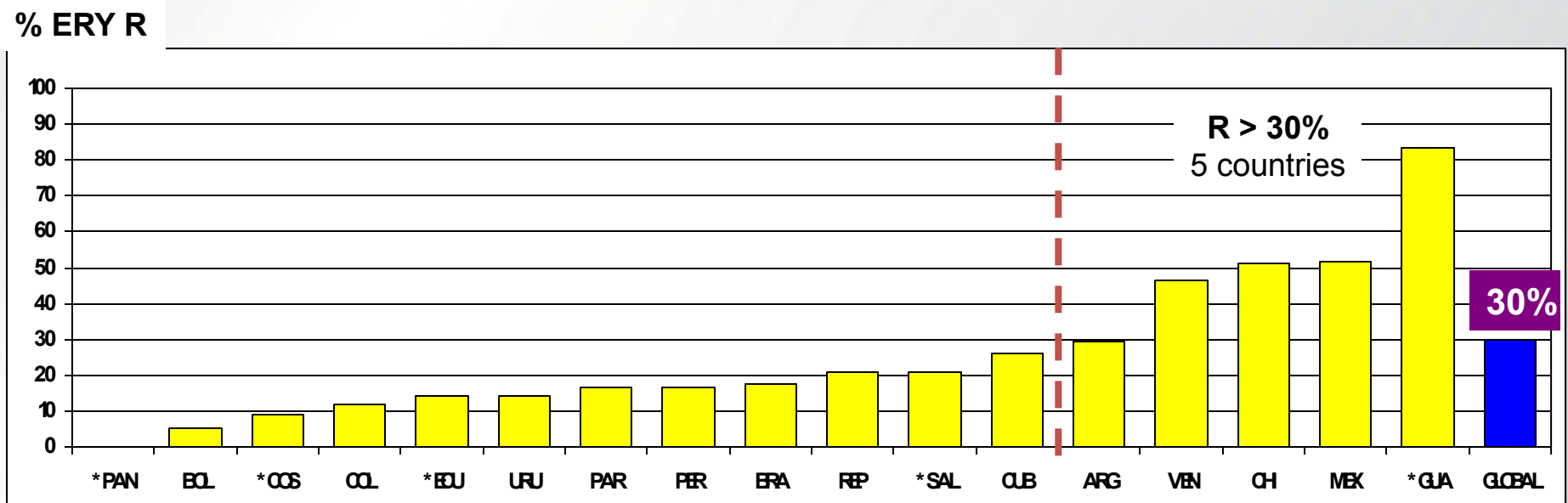
Resistencia (R + I) a la **ceftriaxona** de *S. pn* aislados de casos de meningitis en 2009, criterios CLSI 2008



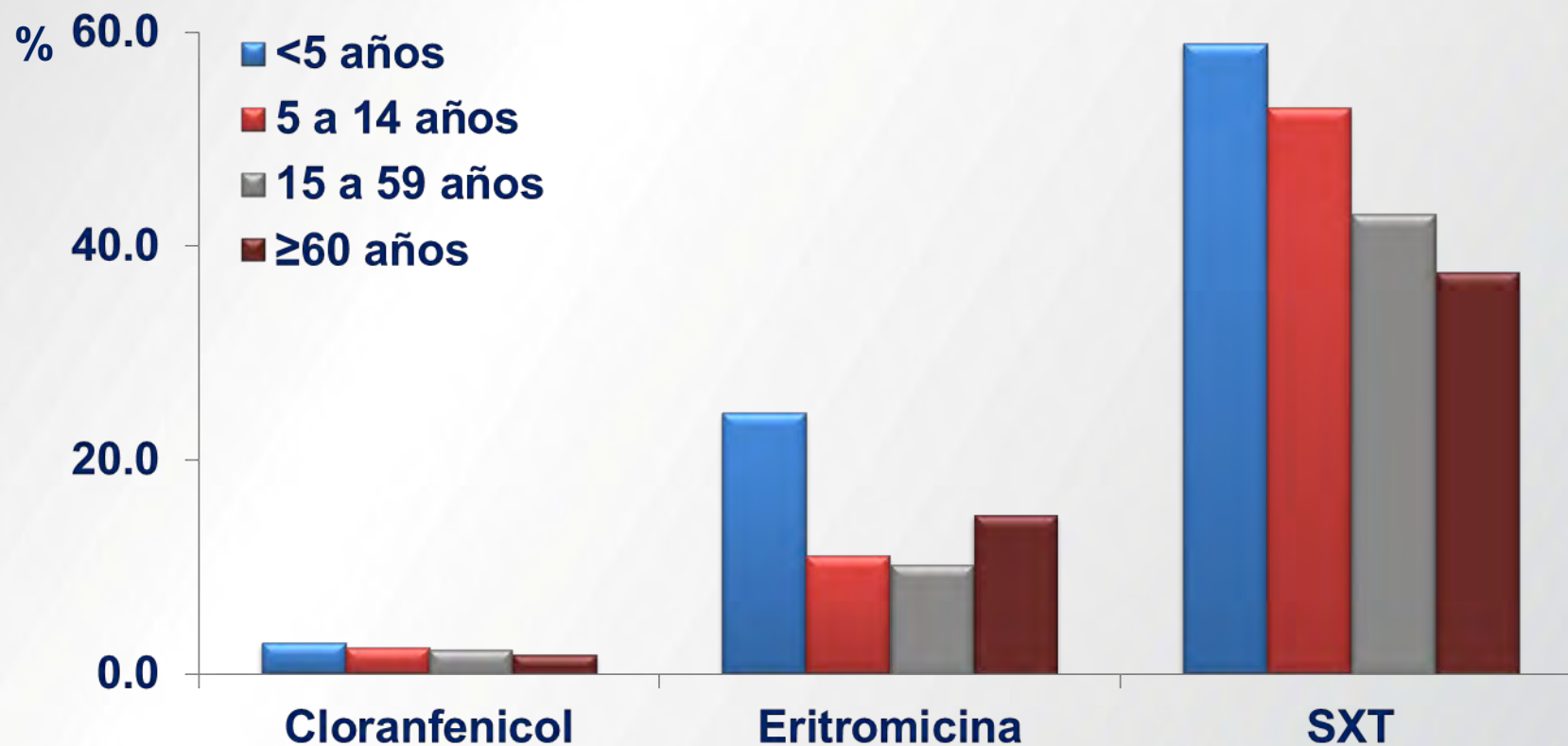
Increasing rates of erythromycin R: ARG, GUA, CUB, MEX, VEN.



Erythromycin resistance in Spn: LA 2010, < 6 yrs old, n: 1426



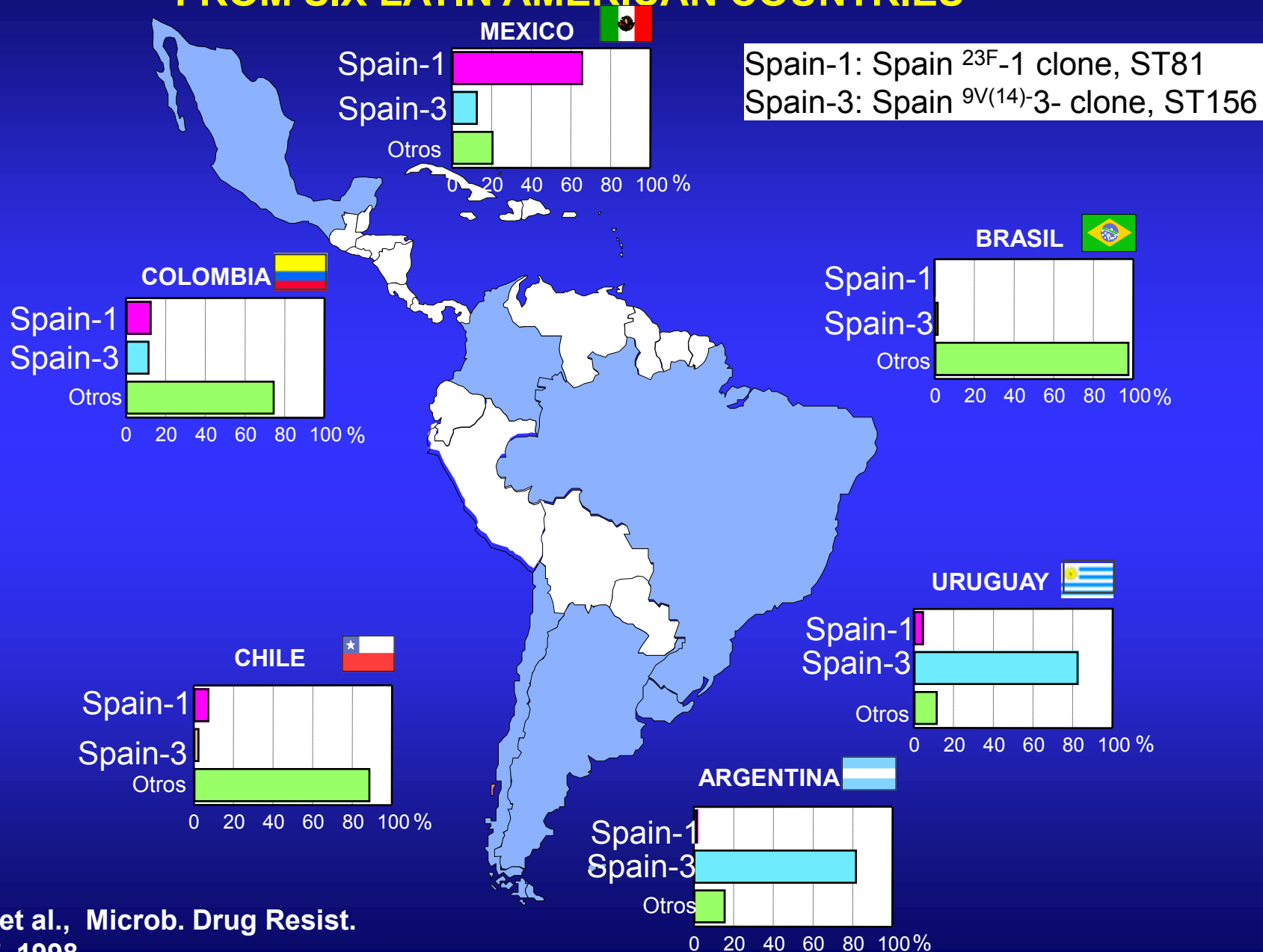
Resistencia de Spn a los antibióticos no beta lactámicos en la región , 2006-2010



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INTERNATIONAL CLONES AMONG PENICILLIN-RESITANT ISOLATES FROM SIX LATIN AMERICAN COUNTRIES



SPREAD of Spain ^{23F}-1 – ST81 and Spain ^{9V(14)}-3- ST156 clones in LATIN AMERICAN COUNTRIES

● Spain ^{23F}-1 clone
ST81
6 countries:
ARG
MEX
CHI
COL
PAR
URU



● Spain ^{9V(14)}-3- clone
ST156
8 countries:
ARG
BRA
CHI
COL
CUB
MEX
PAR
URU

Main clone associated
with DSP

Serotypes and Clonal Types of Penicillin-Susceptible *Streptococcus pneumoniae* Causing Invasive Disease in Children in Five Latin American Countries

HELENA ŽEMLIČKOVÁ,^{1,8,9} M. INÊS CRISÓSTOMO,^{1,9} MARIA C. BRANDILEONE,² TERESA CAMOU,³
ELISABETH CASTAÑEDA,⁴ ALEJANDRA CORSO,⁵ GABRIELA ECHÁNIZ-AVILES,⁶
MÓNICA PÁSZTOR,⁷ and ALEXANDER TOMASZ¹

- **185** PEN-S, 2000-2002: ARG, BRA, COL, MEX, URU
- Serotypes 14, 6B, 5, 1, 23F- 7F, 3

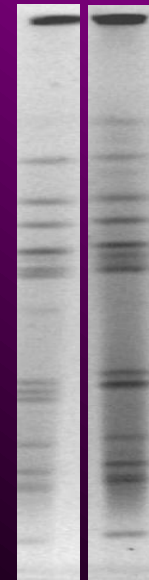
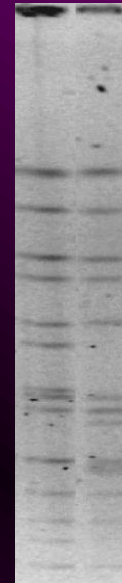
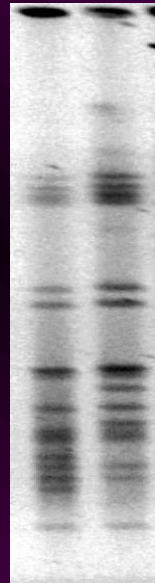
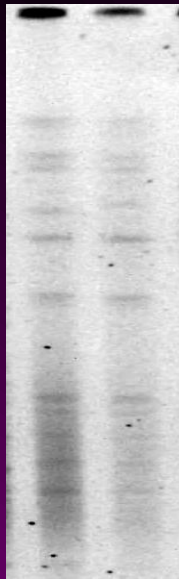
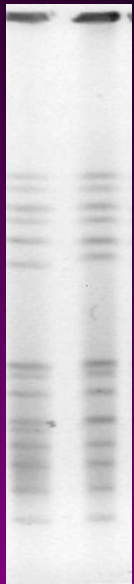
- ST289 (serotype 5) / Colombia⁵-19
 - ST191 (serotype 7F)/ Netherlands^{7F}-39
 - ST242 (serotype 23F)/Taiwan^{23F}-15
 - ST304 (serotype 1)/Sweden¹-40
- } 40%

- Important differences between serotypes....

Spn clones associated with macrolide resistance

88% SPN: 5 International Clones

PFGE-SmaI - MLST



England¹⁴⁻⁹
(42%)
ST9

Poland^{6B-20}
(20%)
ST315

Spain^{9V-3}
(16%)
ST156

Spain^{6B-2}
(6%)

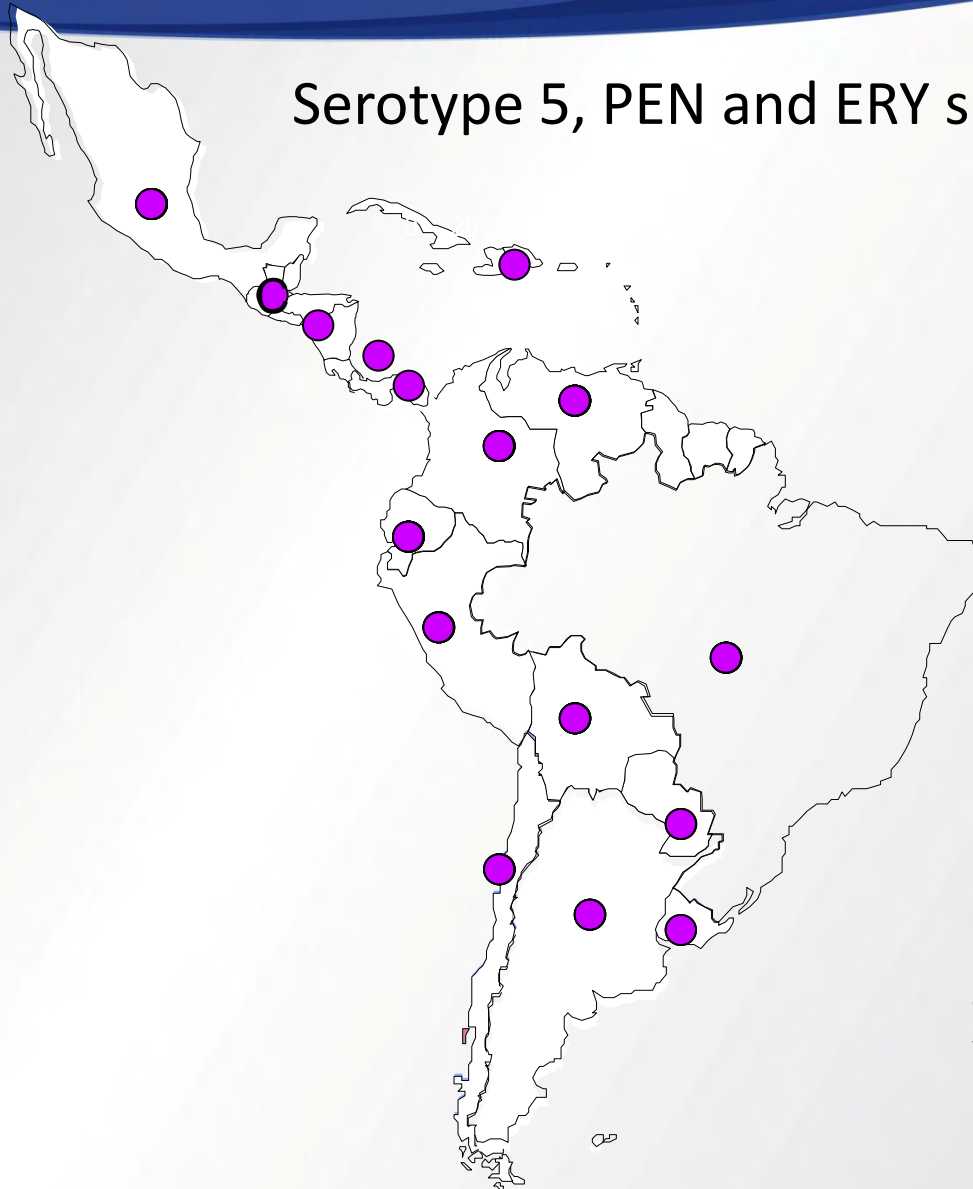
Spain^{23F-1}
(4%)

78% (*mef A* or *erm B*)

Serotype 5 in Latin American countries : Colombia ⁵-19- ST289 clone

Serotype 5, PEN and ERY susceptible but

resistant to TET/CMP/SXT



● Colombia ⁵-19 clone
ST259

15 countries:

COL - NIC

ARG - MEX

BOL - PAN

BRA - PAR

CHI - PER

DR - URU

ECU - GUA

VEN

Tamayo et al. 1999. JCM.37:2337

Vela, et al. 2001. MDR. 7:153

Gamboa, et al JCM. 2002.40:3942

Moreno, et al. Biom.2003.23:77

Moreno, et al. 2004..Biom. 24:296

Firacative et al. 2006. Biom. 26:295

Firecative et al. Pan Am J Public Health.2009.25:337

Distribution of international clones of *S. pn* in Latin America



Spain ^{23F}- 1- ST81
 Spain ^{6B}- 2- ST90
 Spain ^{9v}- 3- ST156
 Tennessee^{23F}- 4-ST37
 England ¹⁴- 9-ST9
 Taiwan ^{19F}- 14-ST236
 Taiwan ^{23F}- 15-ST242
 Tennessee ¹⁴- 18-ST66
 Colombia ⁵ - 19-ST289
 Poland ^{6B} - 20-ST315
 Portugal ^{19F}- 21-ST51
 Sweden ^{15A}- 25-ST63
 Colombia ^{23F}- 26-ST338
 USA ¹- 29-ST615
 Sweden ¹ -40-ST304

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Conclusions (1)

1. Antibiotic use in Latin America has increased, with some variation between countries; this increased may explain the rise in pneumococcal resistance. **Efforts to optimize antibiotic use should be implemented in the Region**
2. Pneumococcal antimicrobial resistance is more important in children < 5 yrs of age and decreases in older children and adults
3. Antimicrobial resistance, **specially in non-vaccine** serotypes, in older children and adults should be monitored

Conclusions (2)

4. There was an increase of ERY resistance in LA, 30% in 2010. It could be associated to the spread of international clones and increase in the use of macrolides and oral cephalosporin.
5. **Serotype 19A increased in LA in absence of PCVs.** This increase could be attributed to the proliferation of pre-existing clones, and to the increase in the use of macrolides.
6. **Continued surveillance** of dominant clones and antimicrobial susceptibility in LA will contribute to evaluate the influence of the selective pressure of antimicrobial agents and the impact of the introduction of the new PCVs.

Acknowledgments

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❖ **María Elena Realpe, INS, Colombia**

❖ **Alex Tomasz, H. de Lencastre
Laboratory Microbiology
The Rockefeller University, NY**