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Invasive pneumococcal disease at the largest pediatric hospital in Quito – Ecuador, from 2014 to 2018

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Abstract

Introduction: *Streptococcus pneumoniae* (pneumococcus) is still an important cause of pneumonia, sepsis, and meningitis in children worldwide. In Ecuador, there is a paucity of information about the invasive pneumococcal disease.

Methods: This was a retrospective-cohort study that was carried out in the largest pediatric public third-level hospital in Quito, Ecuador. The study was conducted from 2014 to 2018. Medical records of patients with invasive pneumococcal disease (IPD) were analyzed. *S. pneumoniae* serotypes were identified, their antimicrobial susceptibility was assessed, clinical manifestations were determined, and mortality of IPD at a third-level hospital in Quito was stablished, from 2014 to 2018.

Results: Most patients with IPD were under 2 years old. Pneumonia was the most frequent clinical presentation and serotype 19A was the most prevalent. S. *pneumoniae* isolates were resistant in different percentages to clindamycin, erythromycin, trimethoprim sulfametoxazol, penicillin, levofloxacin, ceftriaxone. Meningeal isolates showed a higher frequency of antimicrobial resistance. Although most patients had received a pneumococcal conjugated vaccine against 10 serotypes (PCV10), they still presented IPD.

Discussion: Despite most patients (88.2%) had received a pneumococcal conjugate vaccine against 10 serotypes (PCV10), they still had IPD. S. *pneumoniae* serotype 19A was the most common cause of IPD and showed the highest prevalence of antibiotic resistance in infected children included in this study.

Conclusions: Pneumonia and sepsis were the most common IPD, and serotype 19A was most frequent. National Pneumococcal surveillance by serotype in Ecuador is essential to understand the impact of PCVs in the epidemiology of invasive pneumococcal disease and to assess the effectiveness of immunization programs.

Keywords: *Streptococcus pneumoniae*, invasive pneumococcal disease, serotypes, Ecuador.

Enfermedad invasiva neumococica en el mayor hospital pediátrico de Quito – Ecuador, 2014 to 2018

Resumen

Introducción: *Streptococcus pneumoniae* (neumococo) sigue siendo una causa importante de neumonía, sepsis y meningitis en niños en todo el mundo. En Ecuador, hay escasez de información sobre la enfermedad neumocócica invasiva.

Métodos: Se trata de un estudio de cohorte retrospectivo que se llevó a cabo en el hospital público pediátrico de tercer nivel más grande de Quito, Ecuador. El estudio se realizó entre 2014 y 2018. Se analizaron las historias clínicas de los pacientes con enfermedad neumocócica invasiva (ENI). Se identificaron serotipos de *S. pneumoniae*, su susceptibilidad antimicrobiana, manifestaciones clínicas y mortalidad de ENI en un hospital de tercer nivel en Quito, de 2014 a 2018.

Resultados: La mayoría de los pacientes con ENI tenían menos de 2 años. La neumonía fue la presentación clínica más frecuente y el serotipo 19A fue el más prevalente. Los aislados de *S. pneumoniae* fueron resistentes en diferentes porcentajes a clindamicina, eritromicina, trimetoprim sulfametoxazol, penicilina, levofloxacina, ceftriaxona. Los aislados meníngeos mostraron una mayor frecuencia de resistencia a los antimicrobianos. Aunque la mayoría de los pacientes habían recibido una vacuna antineumocócica conjugada contra 10 serotipos (PCV10), aún presentaron ENI.

Discusión: A pesar de que la mayoría de los pacientes (88,2%) habían recibido una vacuna antineumocócica conjugada contra 10 serotipos (PCV10), aún tenían ENI. El serotipo 19A de *S. pneumoniae* fue la causa más común de ENI y mostró la mayor prevalencia de resistencia a los antibióticos en los niños infectados incluidos en este estudio.

Conclusiones: Los tipos de ENIs más frecuentes fueron neumonía y sepsis, el serotipo más común fue 19A. Es de extrema importancia reforzar la vigilancia epidemiológica en el país para precisar la realidad de serotipos circulantes y valorar la efectividad e impacto vacunal.

Palabras clave: *Streptococcus pneumoniae,* neumonía; serotipos, Ecuador; Neumonía Neumocócica; Infecciones Neumocócicas

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Introduction

In 2017, the World Health Organization (WHO) included *Streptococcus pneumoniae* (*S. pneumoniae*) as one of the 12 priority pathogens worldwide[1]. *S. pneumoniae* (also known as pneumococcus) is a gram-positive bacterium, with the shape of spherical cocci with a polysaccharide capsule. This capsule is considered critical for its virulence in human infections. Due to capsule variation, more than 90 serotypes have been described[2–5]. The proportion of children who are pneumococcal nasopharyngeal carriers vary from <15% to >90% in different geographical areas. This colonization also varies with age, being higher at 2-3 years (50-80%), and decreasing thereafter to (5-10%) in children older than 10[1,6].

Morbidity and mortality from pneumococcal infections are highest among unvaccinated children under 5 years of age and are an important cause of pneumonia, sepsis, and meningitis[7–12]. In recent years, there has been an increase in pneumococcal antimicrobial resistance that further complicates management in patients infected with these strains[13].

The fight against pneumococcus improved globally with the introduction of the first conjugate pneumococcal vaccine-7 (PCV7) in 2000 that included protection against seven serotypes: 4, 6B, 9V, 14, 18C, 19F, and 23F. Subsequently, the PCV10 was introduced in 2010 and included the serotypes: 1, 3, 7F to the PCV7. Lastly, vaccine PCV13 has been implemented since 2013. This novel vaccine includes protection against 19A, 6A serotypes in addition to the PCV10-antigens vaccine[2–5,9,11,12,14–17]. With the sequential introduction of the indicated vaccines, the phenomenon of "replacement" has occurred through time, which means a decrease in the prevalence of the serotypes included in vaccines and an increase of the serotypes not included in them[2,6,11,12,18,19]; this phenomenon has varied in different regions of the world[7]. For instance, upon the introduction of the PCV10 in Chile, there was an increase in invasive pneumococcal disease (IPD) by serotype 19A, present in PCV13, which is of special importance for its high virulence and antimicrobial resistance[20,21].

Pneumococcal surveillance by serotype is essential to understand the impact of PCVs in the epidemiology of invasive pneumococcal disease and to assess the effectiveness of immunization programs[13,22]. The introduction of PCV10 vaccines has shown several herd protection effects including a decrease of invasive pneumococcal disease, nasopharyngeal carriers, and a modification of the epidemiology of community-acquired pneumonia in non-immunized children and adults[3,4,11,12,19,23].

In Ecuador, PCV7 was introduced in 2008 and PCV10 in 2011 as part of the National Immunization Program. Despite the latter, there are no national data showing the national prevalence of the most frequent pneumococcal serotypes. The vaccine has been administered to 2, 4, and 6 months of age[24,25]. Until 2021, PCV13 was not yet included in the national immunization program in Ecuador. However, PCV13 can be obtained in private medical practice in the country but unfortunately, there are no statistics on the number of children that have received the PCV13 vaccine and the seroprevalence of invasive pneumococcal diseases.

Here we present data on circulating *S. pneumoniae* serotypes from 2014 to 2018, their antimicrobial susceptibility, clinical manifestations, and mortality associated with invasive pneumococcal disease in the largest pediatric hospital in Quito, Ecuador.

Materials and methods

Study design and participants

The retrospective cohort study was performed during January 1, 2014, and December 31, 2018 in the largest pediatric public-third-level hospital in Quito. The medical records of patients with invasive pneumococcal disease were analyzed (IPD). The following variables were considered from the medical records: sociodemographic data, early type of feeding, anti-*S. pneumoniae* vaccination, initial clinical presentation, previous complications of *S. pneumoniae* infection, co-morbidities, and antibiotic therapy. The microbiological characterization of *S. pneumoniae* and antibiotic resistance profile for each patient was extracted from the microbiology laboratory system from the first isolation made per patient. All isolates were serotyped by conventional Quellung reaction method at the US Centers for Disease Control and Prevention *Streptococcus* Laboratory (CDC, Atlanta, GA, US).

Invasive pneumococcal disease was defined as isolation of *S. pneumoniae* in a sterile fluid such as blood, cerebrospinal (CSF), pleural or joint fluids[18,26,27].

We included children with information regarding sociodemographic data, early type of feeding, anti-*S. pneumoniae* vaccination, initial clinical presentation, prior clinical complications due to *S. pneumoniae* infection, co-morbidities, treatments and with *S. pneumoniae* positive cultures from blood, CSF, pleural or joint fluids. Patients without complete information in their medical records were excluded from the study.

Statistical analysis

Descriptive statistics such as frequencies, percentages, means with their standard deviation were calculated with the software SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Ethics

This study was approved by the Ethics Committee of SOLCA Hospital (CEISHSALCAQ.OBS.18.053).

Results

Forty-two patients met the inclusion criteria, there was a similar proportion of participants from both genders; most children were younger than 2 years of age, Table 1. The majority

of participating children had exclusively human milk feeding during the first months of life and were vaccinated against pneumococcus, Table 1.

Invasive pneumococcal disease was manifested most frequently as pneumonia and sepsis, followed by meningitis, and septic arthritis. Also, 19.1% of children presented congenital malformations and 9.5% cancer, and approximately 25% of children had more than two co-morbidities, Table 2. Table 3 shows the frequency of *S. pneumoniae* serotypes by age. We observed that serotype 19A was predominant in all age groups studied, 0-2 years with 61.5%, > 3 and < 4 with 57%, more than 5 years with 44%. Other identified serotypes were less common, Table 3. It is important to note that there has been an important increase in the frequency of serotype 19A between 2016 and 2018, Figure 1.

To identify antibiotic resistance in *S. pneumoniae,* we registered the microbiological characteristics of the clinical isolates which were interpreted according to the recommendations of the M100 protocol of the Clinical and Laboratory Standards Institute (CLSI)[28]. There was a high frequency of antibiotic resistance in several serotypes, Table 4. *S. pneumoniae* serotype 19A presented the greatest resistance to all antibiotics tested, Table 4. Furthermore, serotype 19A showed the highest antibiotic resistance to clindamycin, erythromycin, and trimetroprim sulfametoxazol, Table 5.

Regarding hospitalization days, our study found 10.5 ± 14.1 in patients who died and 30.8 ± 31.7 in patients who survived.

Discussion

This study showed that IPD was more frequent in children younger than 2 years old and that the most frequent clinical presentation was pneumonia. Among the studied population, children with IPD usually had important underlying co-morbidities. *S. pneumoniae* serotype 19A was the most common cause of IPD and showed the highest antibiotic resistance. Remarkably, although most patients had received a pneumococcal conjugate vaccine against 10 serotypes (PCV10), they still presented IPD and this could be due to the phenomenon of "replacement" by serotype 19A.

Similar to our studied cohort, in a multicentric study carried out in 11 public hospitals and 5 private clinics in Lima-Peru, that included 101 cases of invasive pneumococcal disease, children younger than 2 years old had IPD; a similar pattern was also observed in Brazil.[12,29] This data indicates that younger children should be considered at greater risk for IPD.

Studies that have assessed the clinical occurrences of IPD have shown that pneumonia, sepsis and meningitis are the three most prevalent forms of the disease. Thus, a study in Taiwan, in a cohort of 78 patients, showed that 46 presented pneumonia (58.9%), 28 sepsis (35.8%) and 4 meningitis (5.1%)[30]. Similarly, in a multicentric research in 18 hospitals in

Table 1. sociodemographic characteristics of the studied population.

Variables	n	%
Male	22	52.4
Female	20	47.6
0 - 2	26	61.9
>3 <4	7	16.7
>5	9	21.4
Costa	4	9.5
Sierra	32	76.2
Oriente	6	14.3
Exclusive human milk consumption (n=30)		
Yes	25	83.3
No	5	16.7
Pneumococcus Immunization (n=34)		
Yes	30	88.2
No	4	11.8

N= number of patients

Table 2. Clinical characteristics of the study population

Variables	N=42	%
Type of clinical presentation		
Pneumonia	25	59.5
Bacteremia	10	23.8
Meningitis	6	14.3
Septic arthritis	1	2.4
Co-morbidities*		
Congenital malformations	8	19.1
Cancer	4	9.5
Trauma	3	7.1
Other	2	4.8
Total co-morbidities	17	40.5

*Percentage of children with one co-morbidity (40.5); two (16.7); three (9.5)

Table 3.

Serotype	0-2 (n=26)	>3 - <4 (n=7)	>5 (n=9)
10A	1		
13	1		
15A	1	1	
19A	16	4	4
19B	1		
19F	1	1	2
23B	1		
3	2		
6	2		
14		1	
1			1
14A			1
15C			1

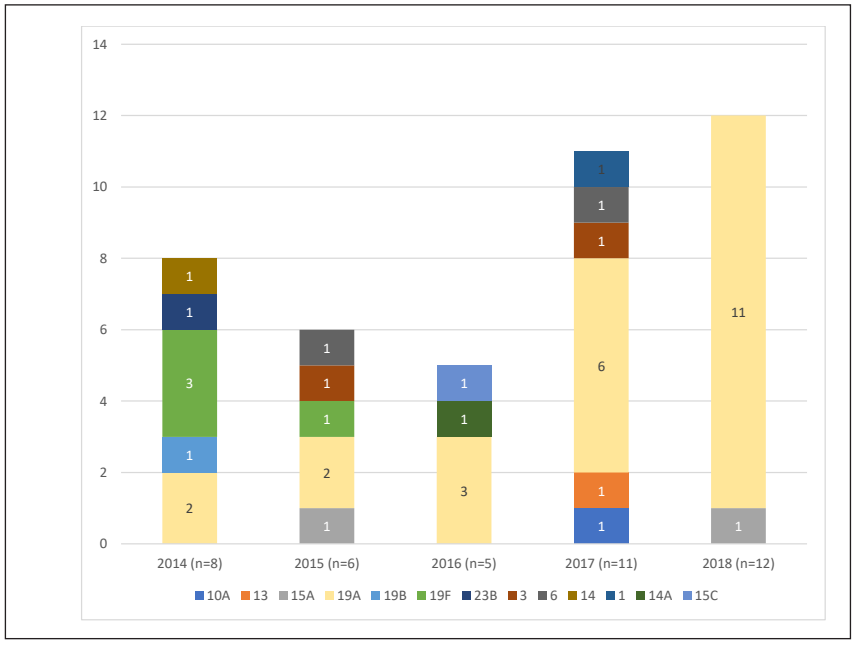

Figura 1. Streptococcus pneumoniae serotypes in pediatric patients with invasive disease in the period 2014 to 2018.

India that included 365 children under 5 years old, 58% had pneumonia, but meningitis was the second most frequent clinical manifestation (35%)[7]. These observations are similar to our findings. It will be important to assess the presence of *S. pneumoniae* in children with these clinical manifestations.

The sequential introduction of different PCVs in the pediatric population, has led to an increase in the prevalence of the *S. pneumoniae* serotypes not included in their composition, the phenomenon of replacement[2,6,11,12,18,19]. For instance, in a systematic review from 38 countries with PCV7, 21.8% of IPD was due to 19A; while in countries with PCV10 or PCV13 in their immunization schedule, serotype 19A was found in 14.2% of cases[15]. Another systematic review included 16 research studies with 2146 patients; 18 serotypes were identified, being 19F the predominating one in 27.7% of cases, followed by 19A with 21.2% of cases[31]. In Brazil, Regis et al, found that out of 82 pneumococcal isolates from sterile body fluids, serotype 14 was the most common (14.6%), followed by 23F (12.2%), 12F (9.8%), 18C (6.1%) and 6B (6.1%) Also, in a prospective study in the United States in 8 pediatric hospitals, which included 482 children, serotypes included in PCV13 were found in 23.9% and not included in PCV13, in 76.1%, mostly 35B, 23B, 33F y 22F. This phenomenon of replacement was also shown in our study, in which serotype 19A predominated 25/42 (59.5%), followed by 19F 4/42 (9.5%), 3: 2 (4.7%) and 6: 2(4.7%)[32]. In Colombia, Camacho et al also reported an increase in serotype 19A incidence in last years in children under 5 years old[33].

Regarding antimicrobial resistance, our study reported resistance to clindamycin in 75% of cases, to erythromycin in 66%, Trimethoprim/sulfamethoxazole in 64%, Penicillins up to 28%, levofloxacin 12%, and Ceftriaxone 9%. On the other hand, 100% of isolates were susceptible to vancomycin. Resistance to penicillins is slightly superior to what Silva-Costa et al observed in Portugal (23.2% - 18.4% low-level resistance and 4.8% high-level resistance) and slightly inferior to values reported in the United States. In the US out of 1498 specimens, the overall PNSP rate was 35% (20% intermediate, 14% resistant), according to nonmeningeal MIC breakpoints, 7.7% of isolates were resistant, with the lowest resistance rates for isolates from blood cultures. 16% of meningeal isolates were resistant to ceftriaxone, and 4.5% of nonmeningeal isolates. MDR major serotypes were 19A, 15A, 6C, and 35B[3]. It is emphasized that in our study serotype 19A resistance to Penicillin was found to be up to 43% of isolates, way up above what Ochoa et al found in Peru (22.8%)[29] and in the upper higher limit range of 12.1–51.9% found in different reports[31].

Global mortality represented 8 cases (19%), which coincides with the range of 10-22% in previous other reports[29,30].

Study strengths and limitations

Strenghts of this study are that it took place in the largest pediatric public health in Quito – Ecuador and number of patients cited.

Most of the patients in the study didn't have a photocopy of vaccination card attached to medical records, verbal information was recollected from parents, which may not be completely reliable.

This study took place in patients from low socioeconomic status at a third-level public pediatric hospital in Quito, which may not represent all the population in the city, nor in the country.

As this was a retrospective study, some data was not included.

Table 4. Resistance

Serotype	TMP (n=29)	ERIT (n=29)	PENIC (n=9)	CEFTRI (n=3)	CLINDA (n=20)	LEVO (n=4)
10A						
13						
15A		1 (3.4%)			1 (5%)	1 (25%)
19A	22 (75.9%)	22 (75.9%)	6 (66.7%)	2 (66.7%)	17 (85%)	3 (75%)
19B	1 (3.4%)	1 (3.4%)	1 (11.1%)			
19F	3 (10.3%)	3 (10.3%)	2 (22.2%)	1 (33.3%)		
23B	1 (3.4%)					
3						
6		2 (6.9%)			1 (5%)	
14	1 (3.4%)					
1						
14A	1 (3.4%)				1 (5%)	
15C						

No resistance to vacomicin was found

Table 5. Antibiotic susceptibility/resistance of *Streptococcus pneumoniae* Serotype 19A

Antibiotic	N	Sensible	Intermediate	Resistant
Trimetoprim Sulfametoxazol	42	13 (31%)		29 (69%)
Vancomycin	42	42 (100%)		0
Erythromycin	41	11 (26.8%)	1 (2.4%)	29 (70.7%)
Penicillin	41	19 (46.3%)	13 (31.7%)	9 (22%)
Ceftriaxone	41	25 (61%)	13 (31.7%)	3 (7.3%)
Clindamycin	28	7 (25%)	1 (3.6%)	20 (71%)
Levofloxacin	33	29 (87.9%)		4 (12.1%)

Future recommendations

We recommend future prospective research in different hospitals in Ecuador to confirm this information. It is recommended that hospitals perform culture, antibiogram and serotyping in patients with suspected pneumococcal disease. If this is not possible in the hospital, they must be sent to a reference laboratory.

High rates of resistance to benzylpenicillin can be expected in different health settings, so in this context each hospital must carry out an antibiotic prescription protocol based on the antibiotic susceptibility profiles in S. pneumoniae adapted to each community.

Conclusions

This study showed that IPD was more frequent in children younger than 2 years old and that the most frequent clinical presentation was pneumonia. *S. pneumoniae* serotype 19A was the most common cause of IPD and showed the highest antibiotic resistance. Remarkably, although most patients had received a pneumococcal conjugate vaccine against 10 serotypes (PCV10), they still presented IPD and this could be due to the phenomenon of "replacement" by serotype 19A. National Pneumococcal surveillance by serotype in Ecuador is essential to understand the impact of PCVs in the epidemiology of invasive pneumococcal disease and to assess the effectiveness of immunization programs.

Ethical disclosures

Acknowledgments. Not applicable

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Ethical issues. This study was approved by the ethics committee of SOLCA Hospital (CEISHSALCAQ.OBS.18.053).

Declaration of Competing Interest. María Quines was a pediatric infectious diseases specialist at Hospital Baca Ortiz during the preparation of this work and became a GSK Vaccines employee during the publication development. She declares current financial and non financial relationship and activities with GSK.

None of the rest of the members of the research team has a conflict of interests or is acting on behalf a third party.

References

1. Weiser JN., Ferreira DM., Paton JC. Streptococcus pneumoniae: transmission, colonization and invasion. Nature Reviews Microbiology. 2018:1–13, doi: 10.1038/s41579-018-0001-8.
2. Plotkin S., Orenstein W., Offit P., K E. Plotkin's Vaccines. Seventh. Philadelphia: Elsevier; 2018.
3. Richter S., Diekema D., Heilmann K., Dohrn C., Riahi F., Doern G. Changes in Pneumococcal Serotypes and Antimicrobial Resistance after Introduction of the 13-Valent Conjugate Vaccine in the United. Antimicrobial Agents and Chemotherapy. 2014;58(11):6484–9, doi: 10.1128/AAC.03344-14.
4. Sharma D., Baughman W., Holst A., Thomas S., Jackson D., Carvalho G., et al. Pneumococcal Carriage and Invasive Disease in Children Before Introduction of the 13-valent Conjugate Vaccine : Comparison With the Era Before 7-valent Conjugate Vaccine. The Pediatric Infectious Disease Journal. 2013;32(2):45–53, doi: 10.1097/INF.0b013e3182788fdd.
5. Shi W., Zhou K., Yuan L., Meng Q., Dong F., Gao W., et al. Serotype distribution, antibiotic resistance pattern and molecular characteristics of serogroup 6 Streptococcus pneumoniae isolates collected from Chinese children before the introduction of PCV13. Journal of Global Antimicrobial Resistance. 2017;13:1–24, doi: 10.1016/j.jgar.2017.12.007.
6. Menezes A., Azevedo J., Leite M., Campos L., Cunha M. Nasopharyngeal carriage of Streptococcus pneumoniae among children in an urban setting in Brazil prior to PCV10 introduction. Vaccine. 2016;34(6):791–7, doi: 10.1016/j.vaccine.2015.12.042.
7. Manoharan A., Manchanda V., Balasubramanian S., Lalwani S., Modak M., Bai S., et al. Invasive pneumococcal disease in children aged younger than 5 years in India : a surveillance study. The Lancet. 2016;3099(16):1–8, doi: 10.1016/S1473-3099(16)30466-2.
8. Bosch AATM., Houten MA Van., Bruin JP., Bogaert D., Rots NY., Sanders EAM. Nasopharyngeal carriage of Streptococcus pneumoniae and other bacteria in the 7th year after implementation of the pneumococcal conjugate vaccine in the Netherlands. Vaccine. 2016;34:531–9, doi: 10.1016/j.vaccine.2015.11.060.
9. Potin M., Fica A., Wilhem J., Cerda J., Contreras L., Escobar C., et al. Opinión del comité consultivo de inmunizaciones sociedad chilena de infectología. Vacuna neumocóccica conjugada en niños y la emergencia de serotipo 19A. Revista Chilena de Infectologia. 2016;33(3):304–6, doi: 10.4067/S0716-10182016000300009.

10. Calbo E., Diaz A., Canadel E., Fabrega J., Uriz S. Invasive pneumococcal disease among children in a health district of Barcelona : early impact of pneumococcal conjugate vaccine. Clinical Microbiology and Infection. 2006;12:867–72, doi: 10.1111/j.1469-0691.2006.1502.
11. Nhantumbo AA., Weldegebriel G., Katsande R., De L., Cuco AZ., Come CE., et al. Surveillance of impact of PCV-10 vaccine on pneumococcal meningitis in Mozambique, 2013 – 2015. Plos One. 2017;12(6):1–12, doi: 10.1371/journal.pone.0177746.
12. Regis C., Azevedo J., Santos V., Moreno-carvalho O., Neves J., Nascimento-carvalho C. Clinical and bacteriological characteristics of invasive pneumococcal disease after pneumococcal 10-valent conjugate vaccine. The Brazilian Journal of Infectious Diseases. 2015;20(1):56–60.
13. Richer S.., Diekema D., Heilmann k., Dohrn k., Riahi F., Doern G. Changes in pneumococcal serotypes and antimicrobial resistance after introduction of the 13-valent conjugate vaccine in the United States. Antimicrobial agents and chemotherapy. 2014;58(11):6484–9, doi: 10.1128/AAC.03344-14.
14. Kaplan SL., Barson WJ., Lin L., Romero JR., Bradley JS. Invasive Pneumococcal Disease in Children ' s Hospitals : 2014 – 2017. Pediatrics. 2019;144(3):2014–7, doi: 10.1542/peds.2019-0567.
15. Balsells E., Guillot L., Nair H., Kyaw MH. Serotype distribution of Streptococcus pneumoniae causing invasive disease in children in the post-PCV era : A systematic review and meta-analysis. Plos One. 2017;12(5):1–20.
16. Kimberlin D., Brady M., Jackson M., Long S. Red Book, Report of the Committee on Infectious Diseases. 31st Editi. Itasca - Illinois: American Academy of Pediatrics; 2018.
17. Ahn JG., Choi SY., Kim DSOO., Kim KIH. Changes in pneumococcal nasopharyngeal colonization among children with respiratory tract infections before and after use of the two new extended-valency pneumococcal conjugated vaccines. Infectious Diseases. 2015;47:385–92, doi: 10.3109/00365548.2014.1001997.
18. Camacho-Moreno G., Imbachi LF., Leal AL., Moreno VM., Patiño JA., Gutiérrez IF., et al. Emergence of Streptococcus pneumoniae serotype 19A (Spn19A) in the pediatric population in Bogotá , Colombia as the main cause of invasive pneumococcal disease after the introduction of PCV10. Human Vaccines & Immunotherapeutics. 2020;00(00):1–7, doi: 10.1080/21645515.2019.1710411.
19. Vestjens SMT., Wagenvoort GHJ., Grutters JC., Meek B., Aldenkamp AF., Vlaminckx BJM., et al. Changes in pathogens and pneumococcal serotypes causing community-acquired pneumonia in The Netherlands. Vaccine. 2017;(June):1–7, doi: 10.1016/j.vaccine.2017.06.049.
20. Ahn G., Choi S., Kim K., Kim D. Changes in pneumococcal nasopharyngeal colonization among children with respiratory tract infections before and after use of the two new extended-valency pneumococcal conjugated vaccines. Infectious diseases (London, England). 2015;47(6):385–92, doi: 10.3109/00365548.2014.1001997.
21. Calbo E., Díaz A., Cañadell E., Fábrega J., Uriz S., Xercavins M., et al. Invasive pneumococcal disease among children in a health district of Barcelona: early impact of pneumococcal conjugate vaccine. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2006;12(9):867–72, doi: 10.1111/J.1469-0691.2006.1502_1.X.
22. Leite C., Azevedo J., Galvao L.., Moreno-Carvalho O., Reis J., Nascimento-Carvalho J. Clinical and bacteriological characteristics of invasive pneumococcal disease after pneumococcal 10-valent conjugate vaccine implementation in Salvador, Brazil. The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases. 2016;20(1):56–60, doi: 10.1016/J.BJID.2015.10.005.
23. Artiles F., Horcajada I., Canas A., Alamo I., Bordes A. Aspectos epidemiologicos de la enfermedad neumococica invasiva antes y despues del uso de la vacuna neumococica conjugada en Gran Canaria. Enfermedades Infecciosas y Microbiologia Clinica. 2009;27(1):14–21, doi: 10.1016/j.eimc.2008.03.001.
24. Ecuador, Ministerio de Salud Pública, Coordinación general de desarrollo estratégico en Salud, Estudio de costo efectividad de la vacuna neumocócica conjugada 10-valente (PCV10) versus la vacuna neumocócica: conjugada 13-valente (PCV13) en el Ecuador. Ecuador; 2016, disponible en internet: efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=https%3A%2F%2Fwww.salud.gob.ec%2Fwpcontent%2Fuploads%2F2017%2F01%2Fbolet%25C3%25ADn-ETES_2016.pdf&clen=1479992&chunk=true
25. Ecuador, Ministerio de Salud Pública. Manual De Vacunas Para Enfermedades Inmunoprevenibles. vol. 2019. Ecuador. Disponible en internet: efaidnbmnnnibpcajpcglclefindmkaj/viewer.html?pdfurl=http%3A%2F%2Fwww.calidadsalud.gob.ec%2Fwpcontent%2Fuploads%2Fdownloads%2F2020%2FDoc%2Finmunizaciones%2FACUERDO%2520MINISTERIAL%252063_2019%2520MANUAL%2520DE%2520VACUNAS%2520PARA%2520ENFERMEDADES%2520INMUNOPREVENIBLES.pdf&chunk=true.
26. Lutui F., Paed M., Grant CC., Best E., Howie S. Invasive pneumococcal disease in children in Tonga. The Pediatric Infectious Disease Journal. 2017;36(2):2016–7, doi: 10.1097/INF.0000000000001400.
27. Brotons P., Monsonis M., Selva L., Sant H., Deu J De., Lisboa UN De. High invasiveness of pneumococcal serotypes included in the new generation of conjugate vaccines. Clinical Microbiology and Infection. 2013:6–11.
28. Clinical and Laboratory Standards Institute. M100Ed31 | Performance Standards for Antimicrobial Susceptibility Testing, 31st Edition. [accessed 19 October 2021]. Available at: https://clsi.org/standards/products/microbiology/documents/m100/.
29. Ochoa TJ., Egoavil M., Castillo ME., Reyes I., Chaparro E., Silva W., et al. Invasive pneumococcal diseases among hospitalized children in Lima , Peru. Revista Panamericana de Salud Publica. 2010;28(2):1–3.
30. Chiu N., Chi H., Peng C., Chang H., Huang DT., Chang L. Retrospective study of prognostic factors in pediatric invasive pneumococcal disease. PeerJ. 2017:1–12, doi: 10.7717/peerj.2941.
31. Fu J., Yi R., Jiang Y., Xu S., Qin P., Liang Z., et al. Serotype distribution and antimicrobial resistance of Streptococcus pneumoniae causing invasive diseases in China : a meta- analysis. BMC Pediatrics. 2019;19(424):1–9.
32. Silva-costa C., Brito MJ., Aguiar SI., Lopes JP., Ramirez M. Dominance of vaccine serotypes in pediatric invasive pneumococcal infections in Portugal (2012 – 2015). Scientific Reports. 2019;9(6):1–9, doi: 10.1038/s41598-018-36799-x.
33. Camacho Moreno G., Imbachi LF., Leal AL., Moreno VM., Patiño JA., Gutiérrez IF., et al. Emergence of Streptococcus pneumoniae serotype 19A (Spn19A) in the pediatric population in Bogotá, Colombia as the main cause of invasive pneumococcal disease after the introduction of PCV10. Human Vaccines and Immunotherapeutics. 2020;16(9):2300–6, doi: 10.1080/21645515.2019.1710411.