Archives of Advances in Biosciences 2020:11(2) doi.org/10.22037/aab.v11i2.25010

Review Article

Challenging Approaches in Combating *Streptococcus Pneumonia* Infection

Amin Talebi Bezmin Abadi*

Department of Bacteriology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

Article Information
Received:2019-4-8
Revised: 2019-6-23
Accepted:2019-10-02

Correspondenc
Amin Talebi Bezmin Abadi
Email:Amin.talebi@modares.ac.ir

Cite this article as: Talebi Bezmin Abadi A. Challenging Approaches in Combating Streptococcus Pneumonia Infection. Archives of Advances in Biosciences 2020:11(2)

Abstract

Context: *Streptococcus pneumoniae* [pneumococcus] induces a large variety of the diseases burden such as bacteremia, meningitis, otitis media and pneumonia in human. Among these, the meningitis can be disclosed with long-lost diseases sequelae. Over the last decades, various recommendations and consensus were released to better manage this major respiratory disease.

Evidence Acquisition: However, there is a controversy among the clinicians about the best strategy in dealing with this chronic infection. In brief, using proper antibiotics or conjugate vaccine to battle this bacterium is a critical question for the clinical setting.

Results: Taken together, it seems that the best possible adopted strategy is to apply the pneumococcal conjugate vaccines in management due to the following two reasons: 1) reducing the bacterial antibiotic resistance rates and 2) decreasing the prevalence of pneumoniae mortality and morbidity at global scale

Conclusion: Conclusively, continuous surveillance surveys determining antibiotic resistance seem inevitable to track pneumococcal genetical variable populations for both successful antibiotic therapy and proper vaccination.

Keywords: *Streptococcus Pneumoniae*, Antibiotic Resistance, Vaccine, WHO, Serotype 19A

1. Context

Following the isolation of *Streptococcus pneumonia* [*S. pneumonia*] in 1881's by Louis Pasteur, it seems necessary to observe this bacterium as listed among the bacteria with yet hundreds of unanswered questions. This encapsulated gram-positive diplococci are genetically and phenotypically close to various species of streptococci habituated in the human oral cavity [1]. Notably, the colonization with this bacterium in the upper respiratory system stays asymptomatic in many of the colonized individuals [2]. Clinically, this facultative microbe is responsible for invasive and non-invasive diseases, ranging from mild ones including simple sinusitis to more severe diseases including septicemia and meningitis [3, 4]. The *S. pneumonia* is a bacterium that basically remains commensal in the human nasopharynx; nonetheless, in a certain situations, it becomes pathogen and finally causes severe diseases such as meningitis and pneumonia with relatively higher mortality rates [5, 6]. *S. pneumonia* is estimated to be solely responsible for 35% of all kind of pneumonia [7]. Only in the developing countries, *S. pneumoniae* is a main causative agent of more than one million death after meningitis and sinusitis among children [8]. As already mentioned, there are still large amount of unknown

queries about this bacterium, listed as virulence factors and the pattern of antibiotic resistance. Nowadays, it is widely debated and some have agreed that strain-dependent capsule is an unforgettable virulence factor detected in this microbe [9, 10]. The capsule efficiently helps the pneumococcus to persist while facing active phagocytosis by immune cells, mainly alveolar macrophages [11]. *S. pneumonia* has been known as a dangerous infectious agent for children under 3 years old and also the most controllable bacteria by the vaccine for many years [12]. Morbidity and mortality reported by the colonization of *S. pneumonia* were sharply increased in recent years due to the i) emergence of antibiotic resistance, ii) lack of an ideal vaccine against all clinical strains, iii) increased aged patients with chronic illness and iv) hospitalization [13-15]. To now, there has been two main tools in battle with this persistent microorganism: antibiotic therapy and vaccination [16]. In brief, there is no clear determined strategy for how to deal with this infection in various patients. In this review, the main purpose was to address two items affecting the low success rate in the management of *S. pneumonia* infections. Moreover, likely prospective of this infection was concentrated on.

2. Evidence Acquisition

2.1 Antibiotics

As expected, antibiotics were applied to eradicate the *S. pneumonia* isolating from clinical samples while the emergence of resistance hampered successful treatment of this bacterium [17, 18]. Regarding bacterial populations, applying inappropriate antibiotics formula resulted in failed therapy and selection of resistant/persistent bacterial clones [antibiotic selection pressure]. Pneumococcal strains are usually exposed to the prescribed antibiotics available in the nasopharynx and mostly propagate in mucosal microniche [19-21]. Among the all gram positive and negative microorganisms, *pneumococcus* is highly potent to receive the new DNA using the transformation approach [22]. This DNA update helped the *pneumococcus* to survive regardless of the environmental antibiotics existence; thus, new offsprings emerged rapidly causing the epidemic pneumoniae among both adults and infants [23, 24]. The problem with streptococci is that human nasopharynx can be an immense territory for commensal bacteria carrying the resistant elements with potency of transforming to the *pneumococcus*. In 1912, Optochin resistance was reported from experimental assays, being an alarming sound for clinical practice concerning difficulty in treating this bacterium in close future [25]. During the 1935s and 1940s, patients with meningitis caused by *S. pneumonia* showed high resistance rate into the sulfonamide [26]. Interestingly, occurrence of resistance to the penicillins lasted until 1968s as reported [27]. Later, resistance to the chloramphenicol was found among the clinical isolates while tetracycline susceptibility rates were also reduced in many of geographical regions [28, 29]. Broadly defined, multidrug-resistant [MDR] pneumococci are characterized by resistance to 3 or more antibiotics at the same time. Although MDR isolates were firstly defined among the pediatric cases, later other research groups were able to identify these classes of antibiotic-resistant strains from the adult groups [30-33]. Reports on antibiotic resistance of *S. pneumonia* to the macrolides have increasingly come into the media and scientific communities. Since *S. pneumoniae* is the first ranked bacterium among causative agents of community-acquired pneumonia, an efficient antibiotic therapy would be preferable by clinicians. To date, the macrolides are the first and most effective choice in elimination of this bacterium in colonized hosts. On the other side, current evidence manifesting the rate of macrolides resistance is getting close to alarming levels in global scale. Previous inappropriate usages of macrolide is the

main risk factor escalating the trend of failed therapy using this antibiotics against *S. pneumonia*. As such, better prescription policies in clinics and increased awareness of patients about the threats of the uncontrolled drug consumptions will be the main solution in this unfair war! Relatively high rate of resistance among the clinical strains of *S. pneumonia* to the cephalosporins and macrolides is a critical concern which needs intensive attention to have better insight into diseases-associated statics about this respiratory system bacterium [19, 20, 34-38].

3. Results

The important rationale for using the vaccine against *S. pneumonia* infection are as follows: i) large burden of aged population in the world, ii) increased health status after proper vaccinations, and iii) lack of proper antibiotic therapy in clinical practice. Having capsular based design is a pitfall for general dissemination of this application among the candidates. From the beginning, pneumococcal conjugated vaccines [PCV] were designed to reduce the prevalence of this persistent bacterium, but rapid emergence of different circulating serotypes led to the defeated vaccines projects worldwide [39-42]. Another basic problem was the decreased immunogenic response to the polysaccharides composition of PCV among the young individuals and also infants. Since twenty years ago, certain proteins were conjugated into the available vaccine, thus T-cell mediated immunity was initiated subsequently [43-45]. The main concern is that despite wide spread usage of PCV, pneumococcal-associated death rate is still increasing, according to the recent WHO released news [46]. In 2014, Tabatabaei *et al* reported that limited success rate of PCV 13, mainly among the young population, is a major threat for public health in Iran. However this finding is contradictory and confirmatory in comparison with different groups [47-50]. Although the status for Iran is quite different, in Japan, the [PCV-7] they announced recommendations for volunteers in order to increase the hygiene situation. In total, introducing the seven-valents PCV [14, 18C, 23F, 19F, 6B, 4 and 9V] conjugate vaccines, which was a main cause of reduced incidence of pneumococcal associated diseases worldwide, was the main cause of the emergence of non-vaccine serotypes of *S. pneumonia*. For example, 19A was a dominant non-vaccine strain which caused pneumonia with high rate of antibiotic resistance [mostly MDR-strains] at national and international levels [51-54]. Moreover, 19A was recently emerged as a dominant serotype with antibiotic resistance among the patients with invasive diseases [55, 56]. A large body of evidence indicate that the universal spread of 19A is a major clinical issue and it needs further attentions, especially in developing and low income countries. Pneumococcus is considered to be the first rank agent in pneumonia acquired from the community in comparison with other human respiratory pathogens. Not only because of failures in establishment of routine antibiotics susceptibility tests in clinical settings, but also for inconsistent national programs, there is no clear guideline to address this problematic and killing diseases, especially for children under 2-4 years old, mainly in developing countries. Although it is more than a century that the scientists have knowledge about the *S. pneumonia*, still the questions exist about how to manage this infection among the patients especially high risk individuals. It is frequently stated that nasopharyngeal carriage of pneumococcal isolates is the main route of transmission into new hosts [57-59]. Therefore, determining the circulating serotypes among the vaccine-target persons would be a novel strategy before starting the vaccination projects, particularly in developing and low-income countries. Presently, most of attempts to produce a preventive vaccine were devoted to suggest a conjugate vaccine; and yet in reality,

pneumococcal diseases, mainly with invasive prognosis, pose huge death rates worldwide. The first available idea is to shift in strategy to produce a vaccine from conjugate to the novel alternative ones. Using the proteins in combination with selective bacterial antigen is a new era which may answer today's frequent queries in the management of pneumococcal-associated diseases. Last but not least, continuous follow-up programs about antibiotic resistance are necessary to track pneumococcal genetical variable populations for both a successful antibiotic therapy and proper vaccination.

4. Conclusion

The antibiotic resistance of *S. pneumoniae* has become a major public health dilemma, even for developed countries. In this line, countries such as the United States reported that the prevalence of drug-resistant strains has increased and in response with this problem, different strategies to compensate are required.

Acknowledgment

The contents of this review is the sole responsibility of the author and do not necessarily represent the official views of any institute or organization. Additionally, I would like to kindly thank the editor/reviewers for their constructive comments.

Conflict of Interest

The authors declare no conflict of interest.

References:

1. Sleeman KL, Daniels L, Gardiner M, Griffiths D, Deeks JJ, Dagan R, et al. Acquisition of Streptococcus pneumoniae and nonspecific morbidity in infants and their families: a cohort study. The Pediatric infectious disease journal. 2005;24:121-7.
2. van Deursen AM, van den Bergh MR, Sanders EA, Group CPS. Carriage of Streptococcus pneumoniae in asymptomatic, community-dwelling elderly in the Netherlands. Vaccine. 2016;34:4-6.
3. Henriques-Normark B, Tuomanen EI. The pneumococcus: epidemiology, microbiology, and pathogenesis. Cold Spring Harbor perspectives in medicine. 2013;3:a010215.
4. Janoir C, Lepoutre A, Gutmann L, Varon E, editors. Insight into resistance phenotypes of emergent non 13-valent pneumococcal conjugate vaccine type pneumococci isolated from invasive disease after 13-valent pneumococcal conjugate vaccine implementation in France. Open forum infectious diseases; 2016: Oxford University Press.
5. Lynch III JP, Zhanel GG. Streptococcus pneumoniae: epidemiology and risk factors, evolution of antimicrobial resistance, and impact of vaccines. Current opinion in pulmonary medicine. 2010;16:217-25.
6. Lexau CA, Lynfield R, Danila R, Pilishvili T, Facklam R, Farley MM, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. Jama. 2005;294:2043-51.
7. Van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. New England Journal of Medicine. 2006;354:44-53.
8. Di Guilmi AM, Dessen A. New approaches towards the identification of antibiotic and vaccine targets in Streptococcus pneumoniae. EMBO Rep. 2002;3:728-34.
9. van der Poll T, Opal SM. Pathogenesis, treatment, and prevention of pneumococcal pneumonia. Lancet. 2009;374:1543-56.
10. Kadioglu A, Weiser JN, Paton JC, Andrew PW. The role of Streptococcus pneumoniae virulence factors in host respiratory colonization and disease. Nature reviews Microbiology. 2008;6:288-301.
11. Shenoy AT BT, Gilley RP, Kumar N, Wang Y, Gonzalez-Juarbe N, Hinkle WS, Daugherty SC, Shetty AC, Ott S, Tallon LJ. Streptococcus pneumoniae in the heart subvert the host response through biofilm-mediated resident macrophage killing. PLoS pathogens. 2017;13:e1006582.
12. Lee GM, Kleinman K, Pelton S, Lipsitch M, Huang SS, Lakoma M, et al. Immunization, antibiotic use, and pneumococcal colonization over a 15-year period. Pediatrics. 2017;140:e20170001.

13. Klugman KP. Risk factors for antibiotic resistance in Streptococcus pneumoniae. South African Medical Journal. 2002;92(3).
14. Rider AC, Frazee BW. Community-Acquired Pneumonia. Emergency Medicine Clinics. 2018;36:665-83.
15. Haran JP, Volturo GA. Macrolide Resistance in Cases of Community-Acquired Bacterial Pneumonia in the Emergency Department. The Journal of emergency medicine. 2018.
16. Jansen KU, Knirsch C, Anderson AS. The role of vaccines in preventing bacterial antimicrobial resistance. Nature Medicine. 2018;24:10.
17. Jacobs MR, Koornhof HJ, Robins-Browne RM, Stevenson CM, Vermaak ZA, Freiman I, et al. Emergence of multiply resistant pneumococci. New England Journal of Medicine. 1978;299:735-40.
18. Hyde TB, Gay K, Stephens DS, Vugia DJ, Pass M, Johnson S, et al. Macrolide resistance among invasive Streptococcus pneumoniae isolates. Jama. 2001;286:1857-62.
19. Pfaller MA, Mendes RE, Flamm RK, Jones RN, Sader HS. Ceftaroline activity against multidrug-resistant Streptococcus pneumoniae from US medical centers (2014) and molecular characterization of a single ceftaroline nonsusceptible isolate. Microbial Drug Resistance. 2017;23:571-9.
20. Musher DM. Resistance of Streptococcus pneumoniae to beta-lactam antibiotics. UpToDate, Waltham, MA[accedido el 10 de juilo de 2015][Links]. 2017.
21. McCormick AW, Whitney CG, Farley MM, Lynfield R, Harrison LH, Bennett NM, et al. Geographic diversity and temporal trends of antimicrobial resistance in Streptococcus pneumoniae in the United States. Nature medicine. 2003;9:424.
22. Bergé M, Mortier- Barrière I, Martin B, Claverys JP. Transformation of Streptococcus pneumoniae relies on DprA- and RecA- dependent protection of incoming DNA single strands. Molecular microbiology. 2003;50:527-36.
23. Majewski J, Zawadzki P, Pickerill P, Cohan FM, Dowson CG. Barriers to genetic exchange between bacterial species: Streptococcus pneumoniae transformation. Journal of Bacteriology. 2000;182:1016-23.
24. Kilian M, Riley DR, Jensen A, Brüggemann H, Tettelin H. Parallel evolution of Streptococcus pneumoniae and Streptococcus mitis to pathogenic and mutualistic lifestyles. MBio. 2014;5:e01490-14.
25. Kilian M, Poulsen K, Blomqvist T, Håvarstein LS, Bek-Thomsen M, Tettelin H, et al. Evolution of Streptococcus pneumoniae and its close commensal relatives. PloS one. 2008;3:e2683.
26. Wester CW, Ariga D, Nathan C, Rice TW, Pulvirenti J, Patel R, et al. Possible overestimation of penicillin resistant Streptococcus pneumoniae colonization rates due to misidentification of oropharyngeal streptococci. Diagnostic microbiology and infectious disease. 2002;42:263-8.
27. Oteo J, Lázaro E, De Abajo FJ, Baquero F, Campos J. Trends in antimicrobial resistance in 1,968 invasive Streptococcus pneumoniae strains isolated in Spanish hospitals (2001 to 2003): decreasing penicillin resistance in children's isolates. Journal of clinical microbiology. 2004;42:5571-7.
28. Dang-Van A, Tiraby G, Acar JF, Shaw WV, Bouanchaud DH. Chloramphenicol resistance in Streptococcus pneumoniae: enzymatic acetylation and possible plasmid linkage. Antimicrobial agents and chemotherapy. 1978;13:577-83.
29. Clewell DB, Gawron-Burke C. Conjugative transposons and the dissemination of antibiotic resistance in streptococci. Annual Reviews in Microbiology. 1986;40:635-59.
30. Whitney CG, Farley MM, Hadler J, Harrison LH, Lexau C, Reingold A, et al. Increasing prevalence of multidrug-resistant Streptococcus pneumoniae in the United States. New England Journal of Medicine. 2000;343:1917-24.
31. Jones RN, Jacobs MR, Sader HS. Evolving trends in Streptococcus pneumoniae resistance: implications for therapy of community-acquired bacterial pneumonia. International journal of antimicrobial agents. 2010;36:197-204.
32. Linares J, Ardanuy C, Pallares R, Fenoll A. Changes in antimicrobial resistance, serotypes and genotypes in Streptococcus pneumoniae over a 30-year period. Clinical Microbiology and Infection. 2010;16:402-10.
33. Navidinia M, Goudarzi M. Overview Perspective of Bacterial Strategies of Resistance to Biocides and Antibiotics. Archives of Clinical Infectious Diseases. 2019;14(2).
34. Verghese VP, Veeraraghavan B, Jayaraman R, Varghese R, Neeravi A, Jayaraman Y, et al.

Increasing incidence of penicillin-and cefotaxime-resistant Streptococcus pneumoniae causing meningitis in India: Time for revision of treatment guidelines? Indian journal of medical microbiology. 2017;35:228.
35. Kim D, Ahn JY, Lee CH, Jang SJ, Lee H, Yong D, et al. Increasing Resistance to Extended-Spectrum Cephalosporins, Fluoroquinolone, and Carbapenem in Gram-Negative Bacilli and the Emergence of Carbapenem Non-Susceptibility in Klebsiella pneumoniae: Analysis of Korean Antimicrobial Resistance Monitoring System. Annals of laboratory medicine. 2017;37:231-9.
36. Bojang A, Camara B, Cox IJ, Oluwalana C, Lette K, Usuf E, et al. Long-term Impact of Oral Azithromycin Taken by Gambian Women During Labor on Prevalence and Antibiotic Susceptibility of Streptococcus pneumoniae and Staphylococcus aureus in Their Infants: Follow-up of a Randomized Clinical Trial. Clinical infectious diseases. 2018:ciy254.
37. Raddaoui A, Tanfous FB, Chebbi Y, Achour W, Baaboura R, Benhassen A. High prevalence of multidrug resistant international clones among macrolide resistant Streptococcus pneumoniae strains in immunocompromised Patients in Tunisia. International journal of antimicrobial agents. 2018.
38. El Moujaber G, Osman M, Rafei R, Dabboussi F, Hamze M. Molecular mechanisms and epidemiology of resistance in Streptococcus pneumoniae in the Middle East region. Journal of medical microbiology. 2017;66:847-58.
39. Almeida AF, Sobrinho-Simões J, Ferraz C, Nunes T, Vaz L. Pneumococcal pneumonia vaccine breakthroughs and failures after 13-valent pneumococcal conjugated vaccine. The European Journal of Public Health. 2016;26:887-9.
40. Oligbu G, Hsia Y, Folgori L, Collins S, Ladhani S. Pneumococcal conjugate vaccine failure in children: a systematic review of the literature. Vaccine. 2016;34:6126-32.
41. Choi C-W, Park EC, Yun SH, Lee S-Y, Kim SI, Kim G-H. Potential usefulness of Streptococcus pneumoniae extracellular membrane vesicles as antibacterial vaccines. Journal of immunology research. 2017;2017.
42. Ladhani SN, Collins S, Djennad A, Sheppard CL, Borrow R, Fry NK, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. The Lancet Infectious Diseases. 2018;18:441-51.
43. Adamkiewicz TV, Silk BJ, Howgate J, Baughman W, Strayhorn G, Sullivan K, et al. Effectiveness of the 7-valent pneumococcal conjugate vaccine in children with sickle cell disease in the first decade of life. Pediatrics. 2008;121:562-9.
44. Madhi SA, Adrian P, Kuwanda L, Jassat W, Jones S, Little T, et al. Long-term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficient virus infected and non-infected children in the absence of a booster dose of vaccine. Vaccine. 2007;25:2451-7.
45. Kadioglu A, Weiser JN, Paton JC, Andrew PW. The role of Streptococcus pneumoniae virulence factors in host respiratory colonization and disease. Nature Reviews Microbiology. 2008;6:288.
46. World Health Organization [WHO]. Estimated Hib and pneumococcal deaths for children under 5 years of age, 2008. http://www.who.int/immunization/monitoring_surveillance/burden/estimates/Pneumo_hib/en. Accessed 16 May 2016. 2016.
47. Tabatabaei SR, Fallah F, Shiva F, Shamshiri A, Hajia M, Navidinia M, et al. Multiplex pcr assay for detection of pneumococcal serotypes in nasopharyngeal samples of healthy children; tehran, 2009-2010. Annual Research & Review in Biology. 2014:3780-90.
48. Tabatabaei SR, Rahbar M, Alam AN, Fallah F, Hashemi A, Yousefi M, et al. Detection of pbp2b gene and antimicrobial susceptibility pattern of Streptococcus pneumoniae isolates in Tehran hospitals, Iran. Archives of Pediatric Infectious Diseases. 2017;5(1).
49. Sakata H. Invasive pneumococcal diseases in children in Hokkaido, Japan from April 2000, to March 2015. Journal of Infection and Chemotherapy. 2016;22:24-6.
50. Sakata H, Sato Y, Toyonaga Y, Hanaki H, Disease DRPSGiPI. Serotype replacement of Streptococcus pneumoniae due to seven- valent pneumococcal conjugate vaccine in Japan. Pediatrics International. 2018;60:52-6.
51. Schroeder MR, Chancey ST, Thomas S, Kuo W-H, Satola SW, Farley MM, et al. A Population-Based Assessment of the Impact of 7-and 13-Valent Pneumococcal Conjugate Vaccines on Macrolide-Resistant Invasive Pneumococcal Disease: Emergence and Decline of Streptococcus pneumoniae Serotype 19A

[CC320] With Dual Macrolide Resistance Mechanisms. Clinical Infectious Diseases. 2017;65:990-8.
52. Schweizer I, Blättner S, Maurer P, Peters K, Vollmer D, Vollmer W, et al. New aspects of the interplay between penicillin binding proteins, murM and the two component system CiaRH of penicillin-resistant Streptococcus pneumoniae serotype 19A isolates from Hungary. Antimicrobial agents and chemotherapy. 2017:AAC. 00414-17.
53. Koutouzis EI, Daikos GL, Chatzichristou P, Michos AG, Koutouzi FI, Chrousos GP, et al. Characteristics of Streptococcus pneumoniae serotype 19A isolates from children in the pre and post Conjugate Vaccine Era. Single center experience 1986–2015. Vaccine. 2018;36:5245-50.
54. Mayanskiy N, Savinova T, Alyabieva N, Ponomarenko O, Brzhozovskaya E, Lazareva A, et al. Antimicrobial resistance, penicillin-binding protein sequences, and pilus islet carriage in relation to clonal evolution of Streptococcus pneumoniae serotype 19A in Russia, 2002–2013. Epidemiology & Infection. 2017;145:1708-19.
55. Ricketson LJ, Vanderkooi OG, Wood ML, Leal J, Kellner JD. Clinical features and outcomes of serotype 19A invasive pneumococcal disease in Calgary, Alberta. The Canadian Journal of Infectious Diseases & Medical Microbiology. 2014;25:e71.
56. Lai C-Y, Huang L-M, Lee P-Y, Lu C-Y, Shao P-L, Chang L-Y. Comparison of invasive pneumococcal disease caused by serotype 19A and non-19A pneumococci in children: more empyema in serotype 19A invasive pneumococcal disease. Journal of Microbiology, Immunology and Infection. 2014;47:23-7.
57. Tarragó D, Aguilar L, García R, Gimenez M-J, Granizo J-J, Fenoll A. Evolution of clonal and susceptibility profiles of serotype 19A Streptococcus pneumoniae among invasive isolates from children in Spain [1990-2008]. Antimicrobial agents and chemotherapy. 2011.
58. Pai R, Gertz RE, Beall B. Sequential multiplex PCR approach for determining capsular serotypes of Streptococcus pneumoniae isolates. Journal of clinical microbiology. 2006;44:124-31.
59. Messina AF, Katz-Gaynor K, Barton T, Ahmad N, Ghaffar F, Rasko D, et al. Impact of the pneumococcal conjugate vaccine on serotype distribution and antimicrobial resistance of invasive Streptococcus pneumoniae isolates in Dallas, TX, children from 1999 through 2005. The Pediatric infectious disease journal. 2007;26:461-7.