Unnecessary prescribing of antibiotics to healthy/asymptomatic school-age carriers of potentially pathogenic bacteria

Mirjana Kostić, MD, PhD,
Vladimir Bedeković, MD, PhD,
Biserka Bastijančić-Kokić, MD,
Tomislav Lauc, DMD, PhD.

ABSTRACT

Objectives: To re-draw attention to the unnecessary prescribing of antibiotics.

Methods: We monitored nasopharyngeal colonization by 3 potentially pathogenic bacteria, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type b in 81 children between the ages of 6 and 7 years who attended the same primary school. The children's health status was also monitored, without using antimicrobial treatment for healthy/asymptomatic carriers. Nasopharyngeal swabs were collected on 6 occasions during autumn months, from mid-September to mid-December 2016. The children who fell ill during the study were treated at the Ear, Nose and Throat Clinic, Sisters of Mercy University Hospital Center, Zagreb, Croatia.

Results: Four hundred and sixty-three nasopharyngeal swabs were collected. Each child had at least one positive swab result. Bacterial colonization with *Streptococcus pyogenes* had the highest colonization rate. During the study, 83% of the children were healthy/asymptomatic carriers with no clinical signs of disease, while 17% became ill. The statistical results showed that the increase in all examined bacteria was statistically significant.

Conclusions: Our study results showed that positive bacterial findings in nasopharyngeal swabs from clinically healthy carriers were not an indication for antibiotic therapy.

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Nasopharyngeal (NP) colonization by potentially pathogenic bacteria (PPB), such as *Streptococcus pyogenes* (Group A streptococcus [GAS]), *Streptococcus pneumoniae* (SP), *Haemophilus influenzae* type b (Hib), *Moraxella catarrhalis* (MC), and *Neisseria meningitidis* (NM), is especially high in children under 5 years of age attending day-care centres,[1-3] and common in children aged between 5 and 15 years.[4,5] These pathogens can cause a wide spectrum of illnesses, from upper respiratory tract infection to invasive diseases, or the colonization can be asymptomatic.[6-11] Children who are healthy/asymptomatic carriers (HC) are a potential source of infections, and for that reason many pediatricians often prescribe antibiotics to them for fear of outbreak of a disease and its spread.[12,13]

Methods. This study monitored the incidence of NP colonization by GAS, SP, and Hib in 81 children between the ages of 6 to 7 years, and children health status, without using antimicrobial treatment for HC. Informed consent was obtained from all parents whose children had been included in the study.

The study protocol has been approved by the Committee on Ethics of the Department of Otorhinolaryngology and Head and Neck Surgery, Sisters of Mercy University Hospital Center, Zagreb, Croatia (EP-18818116-11). All procedures in this study, involving human participants, were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Nasopharyngeal swabs (NPS's) were collected in the same primary school from the same number of children; 27 children from each of 3 classes, on 6 occasions, twice monthly, during the autumn months, following the summer holidays, from mid-September to mid-December 2016. No child had been vaccinated with *Pneumoccocal vaccines* or Hib vaccine before the study. These vaccines are not on the list of mandatory vaccines in our country, so parents decide whether to vaccinate their children or not. Standard microbiological procedures were used to identify GAS, SP, and Hib.[14] The children who became ill during the study were treated and monitored at the Ear, Nose, and Throat (ENT) Clinic, Sisters of Mercy University Hospital Center, Zagreb, Croatia and had NPS's collected in the acute phase of the disease, and 5 days after the end of antibiotic therapy.

Statistical analysis. Nasopharyngeal colonization of GAS, SP, and Hib, and all bacteria together showed a trend of growth during 6 points of swab collection.

GAS - growth trend is shown by the linear regression function $y = 5.2 + 5.80 * x$ (y: GAS, x: time); the regression coefficient is statistically significant ($t(4)=29.0$, $p<0.001$).

SP - growth trend is shown by the linear regression function $y = 6 + 3.29 * x$ (y: SP, x: time); the regression coefficient is statistically significant ($t(4)=7.753$, $p=0.0015$).

Hib - growth trend is shown by the linear regression function $y = 4.8 + 2.06 * x$ (y: Hib, x: time); the regression

coefficient is statistically significant (t(4)=7.060, p=0.0021).

All bacteria together - growth trend is shown by the linear regression function y = 16 + 11.14 * x (y: swabs, x: time): the regression coefficient is statistically significant (t(4)=34.883, p<0.001).

In the time period between the 6 NPS collecting, the number of children who fell ill was almost the same, thus, there were no statistically significant differences.

Results. A total of 463 NPS's were collected; from 81 children at the 1st and 2nd visit, 76 children at the 3rd visit, 75 children at the 4th visit, 73 children at the 5th visit, 77 children at the 6th and final visit. Children who were out of school on the date of swab collection were absent for various reasons. Results showed that 83% of included children were HC's, while 17% (13 children) became ill between visits.

The lowest bacterial colonization was recorded in September, at the first swab collection visit (28% of children colonized by GAS, SP, and Hib), and it increased at each subsequent visit. Colonization by all 3 bacteria peaked at the end of the study, in December (**Figure 1A, Figure 1B**); 84% of children were colonized by GAS, SP, or Hib (**Figure 1B**).

Group A streptococcus, SP, and Hib colonized and recolonized the nasopharynx of each HC at different time intervals. Each child had at least one positive NPS during the study. Most positive swabs had a single bacterium isolated (GAS, SP, or Hib), while 2 different bacteria were isolated from 9 NPS's, and 3 bacteria in a single NPS (**Table 1**). Group A streptococcus was the most commonly isolated bacteria at all 6 time points, increasing from 12% at the first visit, to 40% at the final visit. *Streptococcus pneumoniae* increased from 10% at the first visit, to 27% at the final visit, and Hib increased from 6% at the first visit, to 17% at the final visit (**Table 1, Figure 1A**).

Before the onset of the disease 7 of 13 children were

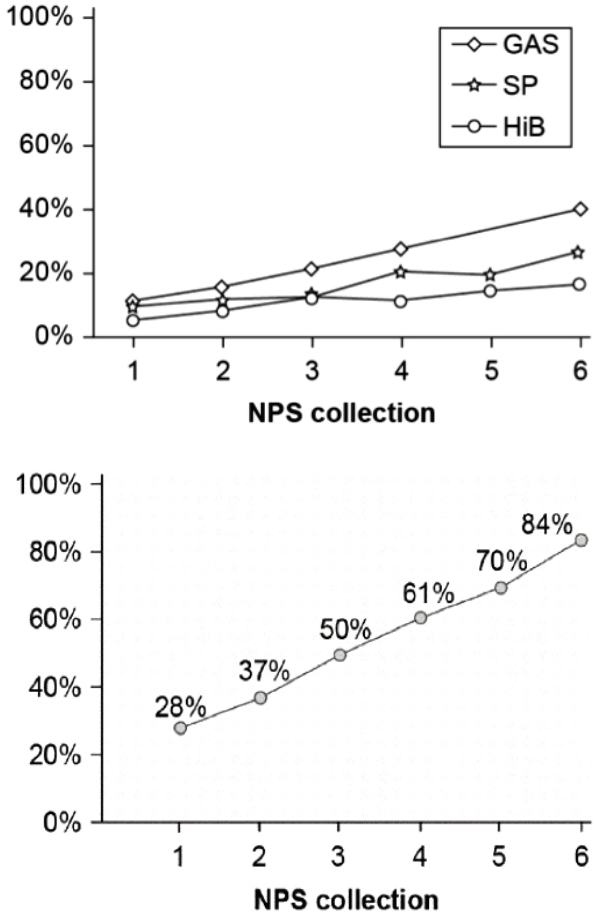

Figure 1 - Graph showing the A) colonization of GAS, SP and Hib at each NPS collection visit and the B) combined colonization of GAS, SP and Hib at each NPS collection visit. GAS - Group A Streptococcus, Hib - *Haemophilus influenzae* type B, NPS - nasopharyngeal swab, SP - *Streptococcus pneumoniae*

Table 1 - Number of present children, and the number and percentage (%) of isolated bacteria in a single nasopharyngeal swab during all 6 nasopharyngeal swab collections.

NPS collection	Children present/ NPS	One bacteria isolated in a single NPS	Two different bacteria isolated in a single NPS	Three different bacteria isolated in a single NPS
1	81	GAS=10 SP=8 Hib=5 n=23 (28%)		
2	81	GAS=13 SP=10 Hib=7 n=30 (37%)		
3	76	GAS=18 SP=10 Hib=10 n=38 (50%)	2 children - GAS, SP	
4	75	GAS=21 SP=16 Hib=9 n=46 (61%)	1 child - GAS, SP 2 children - SP, Hib	
5	73	GAS= 23 SP=15 Hib=13 n=51 (70%)	2 children - GAS, SP 2 children - SP, Hib	1 child - GAS, SP, Hib
6	77	GAS=31 SP=19 Hib=15 n=65 (84%)		
	463 NPS			

GAS - Group A Streptococcus, Hib - *Haemophilus influenzae* type b, NPS - nasopharyngeal swab, SP - *Streptococcus pneumoniae*

Table 2 - Review of 13 children who became ill during the study with diagnoses / Nasopharyngeal swab findings before disease onset, on disease onset, and after antibiotic therapy.

Disease onset on NPS collections	Review of 13 children who became ill during the study	NPS finding before disease onset	NPS finding on disease onset collected at ENT clinic	Diagnosis	Antibiotic therapy yes / no	NPS finding on the 5th day after antibiotic therapy collected at ENT Clinic/	NPS finding on the 5th day after repeated antibiotic therapy collected at ENT Clinic/
1st/2nd	0	0	0	0	0	0	0
2nd/3rd	4 children	NF	GAS	Streptococcal pharyngitis	Yes	GAS- repeated therapy	NF
		NF	SP	AOM	Yes	SP - repeated therapy	NF
		NF	SP	AOM	Yes	NF	
		SP	GAS	Streptococcal pharyngitis	Yes	NF	
3th/4th	3 children	NF	GAS	Streptococcal pharyngitis	Yes	NF	
		GAS	Hib	AOM	Yes	NF	
		SP	GAS	Streptococcal pharyngitis	yes	GAS - repeated therapy	NF
4th/5th	3 children	GAS	GAS	Streptococcal pharyngitis	Yes	NF	
		GAS	Hib	Tonsillitis/pharyngitis	Yes	NF	
		Hib	Hib	Tonsillitis/pharyngitis	Yes	NF	
5th /6th	3 children	NF	GAS	Streptococcal pharyngitis	Yes	GAS - repeated therapy	NF
		NF	Hib	Tonsillitis/pharyngitis	Yes	NF	
		SP	SP	AOM	Yes	SP - repeated therapy	NF

GAS - Group A Streptococcus, Hib - *Haemophilus influenzae* type b, HC - healthy carrier, NF - normal flora, AOM - acute otitis media, ENT - ear, nose, throat, NPS - nasopharyngeal swab, SP - *Streptococcus pneumoniae*

HC's: 3 children were GAS carriers, 3 children were SP carriers, and one child was Hib carrier, without showing any clinical signs of disease (**Table 2**). The same bacteria that were detected before and during the disease were isolated in 3 HC's, while a different bacteria was isolated in 4 HC's (**Table 2**). At the beginning of the illness, a NPS was taken from all of these children at our ENT Clinic. The results showed that all of them had one bacteria in a single NPS and they underwent antibiotic therapy; 6 children had Streptococcal pharyngitis caused by GAS, 4 children had acute otitis media (AOM): 3 AOM caused by SP, one AOM caused by Hib; 3 children had acute tonsillitis/pharyngitis caused by Hib. The duration of antibiotic treatment was determined according to the clinical status of children and the antibiogram. A follow-up NPS taken 5 days after the end of antibiotic therapy showed normal flora (NF) in 8 children, who afterwards rejoined their classes. Group A streptococcus was re-isolated in 3 children who had Streptococcal pharyngitis, SP was re-isolated in 2 children who had AOM. In these children the antibiotic therapy was repeated. A follow-up NPS taken 5 days after the repeated therapy showed NF in all children, and they rejoined their classes (**Table 2**). At the next planed visit, 5 of 13 re-joined children were again HC's without showing any clinical symptoms of disease. One bacterium was isolated in a single NPS in 4 children, and 2 different bacteria were isolated in a single NPS from one child. Since the study ended at the final visit, the number of children that potentially started to show symptoms of illness after that time point is unknown.

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Discussion. Many cases of sporadic outbreaks of diseases in day-care center or schools have prompted antibiotic prescription to whole groups/classes of children in which the outbreaks occurred. Unfortunately, further follow-up swabs following the antimicrobial treatment showed bacterial recolonization in most children.[1-5,12,13] Our study started at the beginning of the school year when children returned from summer holidays and lasted until the beginning of winter holidays (mid-September to mid-December 2016). The results showed a low incidence of NP bacterial colonization at the first and second swab collection visit. The number of carriers increased at each subsequent visit. The highest colonization rates were recorded at the final visit (**Figure 1A, Figure 1B**). The increase in NP bacterial colonization during the study occurred because bacterial transmission between children is much higher when they are at school in close contact with each other, as opposed to when they are on holidays. The statistical treatment of results of the bacterial NP colonization has shown that the increase in all examined bacteria during 6 NPS collections was statistically significant. The children who became ill during the study were treated at

our ENT Clinic with antibiotic therapy, since PPB were isolated in NPS from each of them. It remains unclear why these children became ill during that period rather than earlier or later. This study monitored bacterial colonization, but not the invasiveness of carried strains. In comparison to other studies, our results did not show a significant difference.[1-5,10-13] However, even though many studies related to NP colonization by PPB in children attending day-care centers/schools showed similar results, we have to be aware that the results of future studies may differ from ours. For that reason, we find that such clinical research should continue in order to determine uniform guidelines for the medical treatment of healthy carriers.

In conclusion, our 3-month study monitored the colonization of 3 PPB (GAS, SP, Hib) in nasopharynxes of children attending the same primary school, as well as their health statuses. Statistical evaluation of results has shown statistically significant increase of nasopharyngeal colonization by all 3 examined bacteria. Despite the large number of carriers, especially towards the end of the study (84%), disease outbreaks were sporadic in all 3 classes. Based on our research, we find that positive bacterial findings in NPS's from clinically HC's are not an indication for antibiotic therapy.

The results of our work are meant to help pediatricians in deciding whether or not to prescribe antibiotics to children who are HC's.

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From the School of Medicine (Kostić, Bastijančić-Kokić), Croatian Health Insurance Fund; from the School of Medicine (Bedeković), Department of Otorhinolaryngology and Head and Neck Surgery, Sisters of Mercy University Hospital Center; from the School of Dental Medicine (Lauc), Dental Clinic Apolonia, University of Zagreb, Zagreb, Croatia.

Address correspondence and reprints request to: Mirjana Kostić, School of Medicine, University of Zagreb, Croatian Health Insurance Fund, Zagreb, Croatia. E-mail: micko.mkostic@gmail.com
ORCID ID: https://orcid.org/0000-0001-7315-8165

References

1. Dahlblom V, Soderstrom M. Bacterial interactions in the nasopharynx: Effects of host factors in children attending day-care centers. ***J Infect Public Health*** 2012; 5: 133-141.
2. Puig C, Martil S, Fleites A, Trabazo R, Calatayud L, Li-ares J, et al. Oropharyngeal colonization by nontypable *Haemophilus influenzae* among healthy children attending day care centers. ***Microb Drug Resist*** 2014; 5: 450-455.
3. Wyllie AL, Chu MLJN, Schellens MHB, van Engelsdorp Gastelars J, Jansen MD, van der Ende A, et al. *Streptococcus pneumoniae* in saliva of Dutch primary school children. ***PloS One*** 2014; 9: p.e102045.
4. Magnussen MD, Gaini S, Gislason H, Kristinsson KG. Antibacterial resistance in *Streptococcus pyogenes* (GAS) from healthy carriers and tonsillitis patients and association with antibacterial sale in the Faroe Islands. ***APMIS*** 2016; 124: 327-332.
5. Xu Q, Pichichero ME. Colonization by *Haemophilus influenzae* with *Streptococcus pneumoniae* enhances pneumococcal-specific antibody response in young children. ***Vaccine*** 2014; 32: 706-711.
6. Lamagni T, Guy R, Chand M, Henderson KL, Chalker V, Lewis J, Saliba V, et al. Resurgence of scarlet fever in England, 2014–16: a population-based surveillance study. ***The Lancet Infectious Diseases*** 2018; 18: 180-187.
7. Esposito S, Bianchini S, Baggi E, Fattizzo M, Rigante D. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: an overview. ***Eur J Clin Microbiol Infect Dis*** 2014; 33: 2105-2109.
8. Jervis-Bardy J, Carney AS, Duguidi R, Leachi AJ. Microbiology of otitis media in Indigenous Australian children: review. ***The Journal of Laryngology & Otology*** 2017; 131 (Suppl S2): S2-S11.
9. van Dongen TM, van der Heijden GJ, van Zon A, Bogaert D, Sanders EA, Schilder AG. Evaluation of concordance between the microorganisms detected in the nasopharynx and middle ear of children with otitis media. ***Pediatr Infect Dis J*** 2013; 32: 549-552.
10. Science M, Bitnun A, McIsaac W. Identifying and treating group A streptococcal pharyngitis in children. ***CMAJ*** 2015; 187: 13.
11. Lean WL, Arnup S, Danchin M, Steer AC. Rapid diagnostic tests for group A streptococcal pharyngitis: a metaanalysis. ***Pediatrics*** 2014; 134: 771-781.
12. Zacharioudaki ME, Galanakis E. Management of children with persistent group A streptococcal carriage. ***Expert Rev Anti Infect Ther*** 2017; 15: 787-795.
13. Rutebemberwa E, Mpeka B, Pariyo G, Peterson S, Mworozi E, Bwanga F, and Karin Källander K. High prevalence of antibiotic resistance in nasopharyngeal bacterial isolates from healthy children in rural Uganda: A cross-sectional study. ***Ups J Med Sci*** 2015; 120: 249-256.
14. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing. M100-S25. Wayne (PA): National Committee for Clinical Laboratory Standards; 20015.