

## EPIDEMIOLOGY OF INVASIVE BACTERIAL DISEASES IN CROATIAN CHILDREN BEFORE AND AFTER INTRODUCTION OF VACCINATION AGAINST HAEMOPHILUS INFLUENZAE TYPE B

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*Introduction:* *Haemophilus influenzae type b, Streptococcus pneumoniae, and Neisseria meningitidis were the leading causative agents of invasive bacterial diseases (IBD) among children of less than 5 years of age prior to the introduction of the Haemophilus influenzae type b (Hib) conjugate vaccine. A significant decrease of invasive Haemophilus influenzae diseases (IHD) occurred in nations that implemented routine Hib vaccination in their national immunization program (NIP).*

*Aim:* *The goal of this study was to describe the frequency and characteristics of pediatric patients with IBD before and after routine Hib vaccination was implemented into the Croatian national immunization program (NIP).*

*Subjects and methods:* *A retrospective analysis of patient records from administrative databases for patients aged 0 to 18 with etiologically proven IBD at University Hospital for Infectious Diseases "Dr. Fran Mihaljević".*

*Results:* *A total of 1.112 pediatric patients were analyzed. The patients were divided into three periods: one prevaccinal (reference) and two postvaccinal periods. During the second period, a statistically significant change in proportion occurred for Neisseria meningitidis ( $p < 0.05$ ), Streptococcus agalactiae ( $p < 0.05$ ) and Haemophilus influenzae ( $p < 0.0001$ ). Haemophilus influenzae ( $p < 0.0001$ ) maintained this trend during the third period as well. Additionally, a decrease in Hib meningitis cases was noted ( $p < 0.0001$ ).*

*Conclusion:* *The implementation of Hib vaccine in the Croatian NIP led to a significant decrease of IHD. Streptococcus pneumoniae and Neisseria meningitidis are still the leading causative agents of IBD, and thus the introduction of adequate pneumococcal and meningococcal vaccine in Croatian NIP should be considered.*

Descriptors: CHILDREN, HAEMOPHILUS INFLUENZAE TYPE B, INVASIVE BACTERIAL DISEASES, NEISSERIA MENINGITIDIS, STREPTOCOCCUS PNEUMONIAE, VACCINATION

### Introduction

Invasive bacterial diseases (IBD) are conditions during which microorganisms are identified in bodily fluids that are usually sterile (1). IBD occurs as a consequence of bacterial penetration through anatomical barriers with the

possibility of developing sepsis and focal infections in various tissues and organs. The most susceptible spot for focal infections are joints, bones, pleura, pericardium, brain and the meninges (1, 2).

IBD can also present as occult bacteremia (OB), i.e., the presence of pathogenic bacteria in the blood of a well-appearing febrile child without an identifiable focus of infection (3). After gathering information from patients' medical history and a thorough physical examination, the origin of the infection remains unknown in 20% of children with fever (4). Before the introduction of modern bacterial conjugated vaccines, the most common causative agents of IBD were Streptococcus pneumoniae, Hib and Neisseria meningitidis. The

frequency of IBD caused by these bacteria is age-related and highest in children under 2 years of age (2).

Three factors that predispose for bacteremia in the pediatric population are age, exposure to invasive procedures, and vaccination coverage (5). Firstly, there are age-related diversities in the incidence rate with the highest incidence rate occurring in infants aged 1-11 months (156 per 100.000). Among those aged 5-9 and 10-14 incidence rates dramatically and progressively decrease to 22 per 100.000 and 20 per 100.000, respectively (6). Secondly, the number of invasive procedures used in hospitals and intensive care units (primarily intravenous catheters) increased, thus leading to a change in incidence rates of nosoco-

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mial infections (7). Thirdly, the importance of vaccination coverage. From the beginning of 1990s, European countries began introducing routine early childhood Hib vaccination, thus leading to an effective reduction in Hib infections (8, 9). Due to increased rates of invasive meningococcal disease (IMD) in Europe at the end of the last century, the United Kingdom (UK) became the first country to introduce the meningococcal serogroup C conjugate vaccine (MCC) to their National immunization program (NIP) in 1999, which was followed by a decreased burden of IMD and herd immunity maintenance (8, 10, 11).

*Haemophilus influenzae* (Hi) is a Gram-negative bacteria and exclusively a human pathogen which causes most infections in susceptible individuals. This is why invasive *H. influenzae* diseases (IHD) are considered opportunistic (12, 13). IHD mostly affects children younger than 2 years of age, older patients, and immunocompromized patients (with asplenia, sickle-cell anemia, lymphomas, complement deficiency, etc.), but also healthy children and adults. The most common clinical form of IHD caused by Hib is meningitis, while other common clinical manifestations are bacteremia, sepsis, epiglottitis, cellulitis, septic arthritis, osteomyelitis, pericarditis, and pneumonia. Hib was the leading bacteria that caused acute bacterial meningitis (ABM) in children younger than 5 years of age around the world up to the 1980s (14). *Haemophilus influenzae* may be encapsulated (typeable) and unencapsulated (nontypeable *Haemophilus influenzae*, NTHi). There are six encapsulated serotypes (a, b, c, d, e, and f) that have distinct capsular polysaccharides, their main virulence factor and leading antigen, which prevents complement-mediated bacteriolysis in the absence of opsonizing antibodies. This feature is responsible for higher incidence rates of IHD caused by encapsulated strains. According to various surface antigens, there are six encapsulated Hi serotypes: a, b, c, d, e, and f (12).

Countries that introduced the polysaccharide Hib vaccine in 1985 and conjugate Hib vaccine between 1987 and 1990 into their national immunization

programs (NIP) experienced a dramatic decrease in IHD rates among children younger than 5 years of age (14). The annual incidence of IHD caused by Hib in Europe prior to comprehensive vaccination was approximately 23-41 out of 100.000 children younger than 5 years of age. The most common form was ABM (40-70%) which in 15-30% of cases resulted in hearing loss or some other permanent neurological damage, with a mortality rate of 3-6%. With the introduction of Hib vaccine in 17 European countries, the disease was almost eradicated, and the annual incidence of ABM was reduced to 0-3 out of 100.000 of children younger than 5 years of age (2). The Hib vaccine was introduced into the Croatian NIP in 2002 (2).

Considering the significant reduction of Hib disease in young children due to global vaccination, epidemiological trends for Hib have changed and lately, there is a recorded increase of Hib disease in patients older than 65, as well as an increase in the number of IHD caused by encapsulated non-b serotypes (14, 15). Until recently, the importance of other Hi serotypes in the etiology of IHD was overshadowed by the domination of Hib, but after the introduction of the Hib vaccine, it became evident that other serotypes cause significant morbidity and mortality (12).

*Streptococcus pneumoniae* is a Gram-positive, encapsulated bacteria, that causes mucosal (noninvasive) and invasive infections (16). The most susceptible groups for pneumococcal colonization and infections are children younger than 5 years of age (especially in the range of 3 to 36 months) and patients older than 65 (16). During the first three years of life, more than 60% of children overcome at least one episode of acute otitis media (AOM) and around 30% of children overcome three or more episodes. This is a direct consequence of colonization and infection with various serotypes (17).

Pneumococci are divided into 46 serogroups according to the immune characteristics of the capsule. So far, 94 different antigens have been described, but only a dozen are responsible for as

much as 90% of infections in humans (8). Strains with "higher numbers" are less invasive and more often cause respiratory tract infections without accompanying bacteremia. However, among them, there are those (14, 18C, 19A) which more often cause invasive pneumococcal disease (IPD) (16).

Mucosal infections are mostly respiratory tract infections: AOM, non-bacteremic pneumonia and, in older children, sinusitis. Pneumococci can penetrate into the bloodstream, in which case the mucosal infection becomes the primary focal point of invasive disease (18). Often, invasive and noninvasive pneumococcal diseases cannot be fully clinically separated (18). IPD includes serious clinical syndromes such as (occult) bacteremia, bacterial pneumonia, ABM, pleural empyema, and rarely pericarditis, peritonitis, pyogenic arthritis, osteomyelitis, endocarditis, orbital cellulitis, soft tissue infections, etc. Children in Croatia are frequently admitted to hospital due to IPD, usually bacteremia or bacterial pneumonia and, rarely, pleural empyema and ABM (16). There are two groups of pneumococcal vaccines available in Croatia: pneumococcal polysaccharides 23-valent vaccine (PPV23) and three conjugate vaccines: PCV7, PCV10, and PCV13 which contain 7, 10 and 13 pneumococcal serotypes (Table 1.)

Vaccination with PPV23 is effective for preventing IPD in adults, but its effectiveness decreases over time. A large number of serotypes, among the 23 found in the vaccine, are poorly immunogenic in the group which has the highest incidence of IPD - infants and children younger than 2 years of age (8). PPV23 induces the production of opsonizing antibodies leading to phagocytosis and bacterial lysis, which means that PPV23 does not stimulate immune memory and the reduction of nasopharyngeal colonization with pneumococcus (19).

A heptavalent pneumococcal conjugate vaccine or PCV7, which contains polysaccharide of the seven most common serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F, was approved in Europe in 2001 (8, 19). The introduction of PCV7 led to the reduction of IPD caused by vaccine strains, increased collective

Table 1  
*Pneumococcal vaccines*

Pneumococcal vaccine	Type	Serotypes	Population
PCV7	Conjugate	4, 6B, 9V, 14, 18C, 19F and 23F	Children
PCV10	Conjugate	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5 and 7F	Children
PCV13	Conjugate	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A and 19A	Children, patients >65 years (since August 2014)
PPV23	Polysaccharide	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F	Children >2 years, adults

immunity, reduction of nasopharyngeal colonization and bacterial transmission and decrease of pneumococcal morbidity and mortality in the elderly population but also the increase of pneumococcal pneumonia caused by non-PCV7 strains, which has prompted the production of new pneumococcal vaccines (8, 19). PCV10 is a decavalent vaccine that contains ten serotypes of pneumococcus - those which already include PCV7 and serotypes 1, 5 and 7F (8, 19). In 2010, a new conjugate vaccine was approved - PCV13, with three other additional serotypes: 3, 6A and 19A. In the ten-year period prior to the introduction of PCV13, the number of infections caused by serotype 19A was increasing as well as the resistance to antibiotics, primarily to penicillin and macrolides (8, 19). Although PCV13, as well as other conjugate vaccines, is primarily intended for the prevention of IPD in children, since August 2014 it is also recommended for the vaccination of the elderly population (19).

*Neisseria meningitidis*, or meningococcus, is a Gram-negative bacteria that usually colonizes the nasopharyngeal mucosa. In a small, but significant number of carriers, meningococcus can cause various forms of IMD, usually bacteremia/sepsis and/or meningococcal meningitis. IMD should be suspected in patients that, during the first hours of the disease, develop signs and symptoms that suggest sepsis: fever, general weakness, altered mental state, cold and painful limbs, etc (20). There are 13 meningococcal serogroups. Approximately 90% of IMD is caused by serogroups A, B, and C while the rest is associated with serogroups W, X, and Y (8, 21). Most cases of IMD in Croatia are caused by serogroup B, then by serogroup C while serogroups W and Y are rare (20). A

universal vaccine against all meningococcal serogroups does not exist. European countries that had a high incidence of IMD caused by serogroup C introduced MCC in their NIP. Those countries with increased incidence rates of IMD caused by serogroup B, such as the UK, in 2015 introduced a new vaccine focused on meningococcal outer membrane proteins - 4CMenB. There is still no data about vaccine effectiveness (8). In the USA and some European countries, due to a seroepidemiological difference, a quadrivalent protein-polysaccharide conjugate vaccine that provides protection against serogroups A, C, W, and Y is recommended for people aged between 11 and 55 (8).

*Salmonella* is divided into typhoid and non-typhoid *Salmonella* (NTS). Typhoid *Salmonella* is not a subject of this article. The term "salmonellosis" considers three clinical syndromes: acute gastroenteritis, salmonella fever, and paratuberculosis abdominalis. Salmonellosis is a zoonosis and a food-borne infection. Signs and symptoms of salmonellosis develop 12-72 hours after food intake and consider abdominal cramps, vomiting, diarrhea and fever. More than 50% of patients with salmonellosis are pediatric patients. The younger the age, the greater the susceptibility to a *Salmonella* infection (19).

#### Materials and Methods

This retrospective study analyzed demographic, clinical and laboratory data for a total of 1112 pediatric patients (from 0 to 18 years of age) with etiologically-proven IBD who were hospitalized and treated in the University Hospital for Infectious Diseases (UHID) "Dr. Fran Mihaljević", Zagreb, Croatia, between 1997 and 2014. Since Hib vaccine

was introduced in the Croatian NIP in 2002, we divided our observed period into two periods: the prevaccinal (1st January 1997 - 31st December 2002) and postvaccinal era (1st January 2003 - 31st December 2014). Due to a more credible presentation of the results, the postvaccinal era had to be divided into two periods of different duration. The first period was the reference period for IBD epidemiology prior to the introduction of the Hib vaccine.

Basic statistical calculations were done in Microsoft Excel (Office 2013) and statistical analysis was done in GraphPad Prism 7.00 for Windows 10. Descriptive statistics were made for all of the analyzed variables. Nominal variables are shown as absolute numbers and percentages of specific categories. Quantitative variables are calculated as central tendency measures (median and mean) and appropriate measures of dispersion (interquartile range). The chi-squared test was used to test the interconnection of quantitative variables.

#### Aim

The goal of this study was to describe the frequency and characteristics of pediatric patients with IBD before and after the implementation of routine Hib vaccination into the Croatian NIP, compare the incidence of IBD caused by certain causative agents, and determine the frequency of most common causative agents of IBD in children, their distribution by age group and sex, site of acquired infection, and the most important clinical manifestation. The following predefined data was collected anonymously:

- demographical data (age, sex);
- date of sampling and date of admission;

- leading clinical syndrome/s (bacteremia, sepsis, pneumonia, pleural empyema, acute bacterial meningitis, osteoarthritis, other or combinations);
- samples (blood, cerebrospinal fluid, pleural effusion) and diagnostic methods (cultivation or molecular methods - polymerase chain reaction);
- clinically significant isolated pathogens;
- outcome (complete recovery, improvement, deterioration, lethal outcome or unknown).

### Results

Prior to Hib vaccine introduction, *Neisseria meningitidis*, *Haemophilus influenzae* (type b, type f, and nontypeable) and *Streptococcus pneumoniae* were responsible for nearly the same number of IBD - 71 patients (21.6%), 70 patients (21.3%), and 70 patients (21.3%), respectively. It is followed by *Salmonella* isolated in 25 patients (7.6%) in which *Streptococcus enteritidis* was isolated in 11 cases. Although the number of IMD, IPD, and IHD was almost identical throughout the first period (71, 70, and 70 patients), there is a visible difference in their absolute numbers during the following two periods (Figure 1).

Figure 2 shows absolute numbers of IMD, IPD, and IHD for each year. Before 2002 there was a seemingly equal number (8-15) of patients with IMD, IPD, and IHD per year. After 2002, there has been a gradual decline in the number of IHD, but a striking increase of IPD after 2004.

In order to determine whether the change in proportion to the individual pathogen causing IBD before and after the introduction of the Hib vaccine was statistically significant, the changes in the individual period were compared to those in the reference period (from 1997 to 2014).

Statistical analysis showed that statistically significant changes in IHD ( $p < 0.0001$ ) occurred in the second period and stayed the same in the third period. Also, a statistically significant incre-

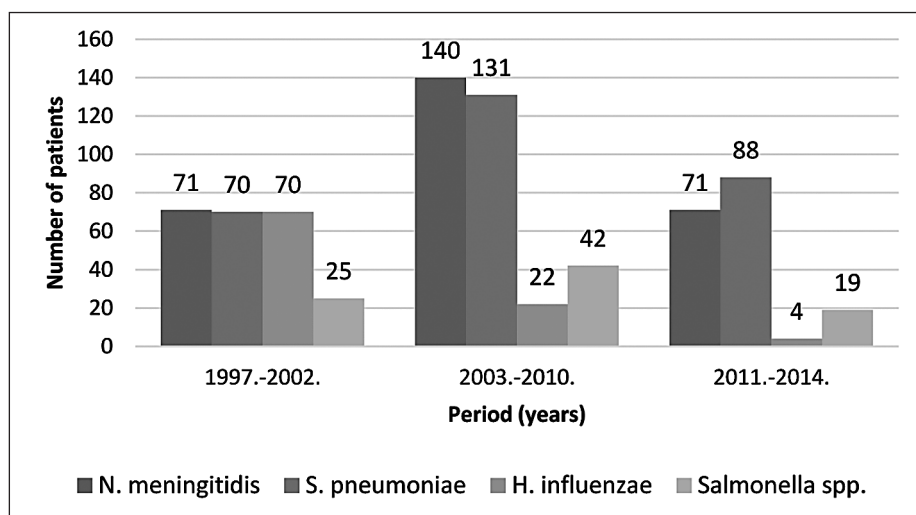


Figure 1  
Number of patients with most frequent IBD throughout the observed periods

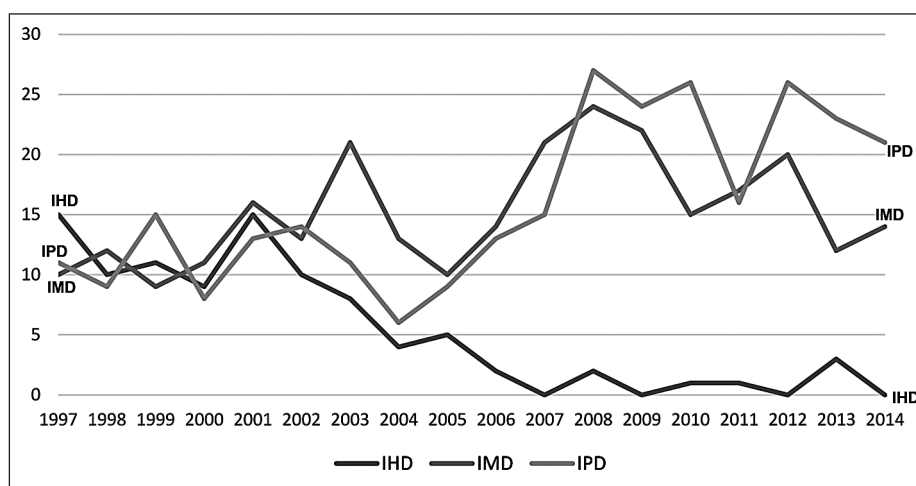


Figure 2  
Absolute number of patients with IHD, IMD, and IPD per year during the observed period

ase of IBD caused by *N. meningitidis* ( $p < 0.05$ ) and GBS ( $p < 0.05$ ) occurred during the second period. Furthermore, an increase of IBD caused by *S. pneumoniae* ( $p < 0.05$ ), *L. monocytogenes* ( $p < 0.0001$ ), and Others/Coinfection ( $p < 0.5$ ) occurred during the third period. Absolute number of IBD caused by a particular causative agent in an eighteen-year period is shown in Table 2.

Prior to vaccine introduction in 2002, the average number of patients with IHD was approximately 11.67 per year, while after 2002 there is a statistically significant decrease of IHD, even to 1 patient per year (Figure 3).

Also, the proportion of patients with IHD caused by Hib in the total number of IHD changed in the observed period. In the reference period, Hib was responsible for 64 (91.43%) IHD, in the second period for 15 (68.18%) ( $p < 0.05$ ) and in the third period for 1 (25%) case of IHD ( $p < 0.0001$ ).

The share of IHD increased due to other serogroups and nontypeable strains. Thus, the share of IHD caused by non-b serogroups increased from 7.14% (5/70) in the period 1997-2002 to 9.09% (2/22) in the period 2003-2010 and in the last period to even up to 50% (2/4) which proved to be statistically significant. ( $p < 0.05$ )

Table 2  
Absolute number of IBD caused by a particular causative agent

Pathogen	1997-2002	2003-2010	2011-2014	Total
N. meningitidis	71	140	71	282
S. pneumoniae	70	131	88	289
H. influenza	70	22	4	96
Salmonella spp.	25	42	19	86
S. aureus	16	29	20	65
E. coli	14	26	8	48
S. agalactiae	1	17	5	23
S. pyogenes	2	5	7	14
L. monocytogenes	7	7	1	15
K. pneumoniae	5	10	7	22
P. aeruginosa	5	6	7	18
Others	42	49	40	131
Coinfection	1	5	17	23
Total	329	489	294	1112

### Discussion

Although Hib polysaccharide vaccine was on the free market in Croatia since 1995, the number of vaccinated children remained too low to make any significant impact on the incidence rate. A lot of countries witnessed a decrease of IHD after the introduction of the Hib vaccine in their NIP, including Croatia. Since 2003, IHD caused by Hib occurs primarily in children who are not fully vaccinated or didn't receive boost doses during the first 12 months. Some acquire the infection before they have been fully vaccinated.

During the vaccination period, there were three cases of meningitis caused by H. influenzae: two cases caused by type f and one caused by type b. The course of disease was favorable in all patients. During this period, 7 infections with NTHi were recorded as well.

Despite a high primary vaccination coverage (>95%) against Hib, sporadic cases of IHD are still possible, but there has been a decline in the overall prevalence of occult bacteremia, particularly in the age group from three to six months. The decline in the overall prevalence of bacteremia comes with a relative

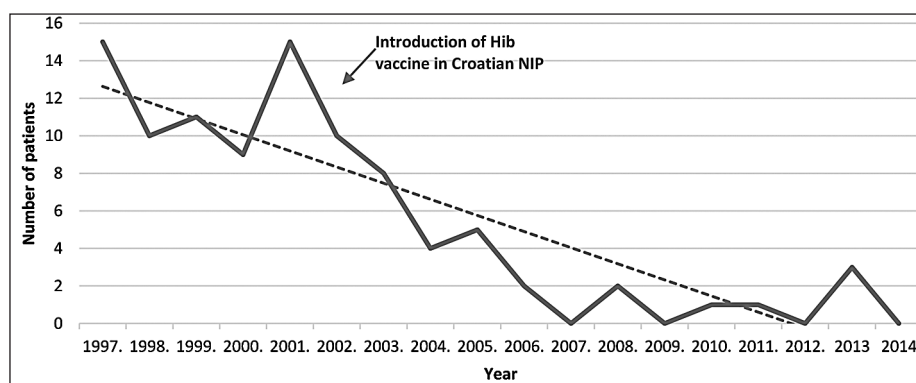


Figure 3  
Number of patients with invasive Haemophilus influenzae type b disease (IHD) per year during the observed period

increase of S. pneumoniae as the cause in >90% of occult bacteremia cases.

Unlike IHD, IMD and IPD were constantly present in almost equal proportions with a slightly increasing incidence. The increased incidence rate of IMD can partly be explained by the use of more precise diagnostic methods (primarily PCR). The increased incidence rate of IPD is most likely the result of a real increase.

### Conclusions

IBDs are still a serious public health problem among Croatian children, even after Hib conjugate vaccines were introduced in the NIP in 2002. S. pneumoniae, N. meningitidis and H. influenzae were the most important causes of IBD before routine vaccination and responsible for almost the same number of cases. After routine vaccination, S. pneumoniae, and N. meningitidis are responsible for a nearly equal number of IBD, while IHD is almost completely eliminated. The introduction of pneumococcal and meningococcal vaccines in the NIP of several countries seems to be the key for IBD control and has equal importance as universal screening for GBS colonization in pregnant women. Pneumococcal seroprevalence monitoring is the key for adequate pneumococcal vaccine selection whose introduction in the Croatian NIP could reduce the incidence of IPD and IBD overall. A vaccine directed against the protein of the meningococcal outer membrane 4CMenB (Bexsero), which was approved by the European Commission, has only recently been introduced in the British NIP. This vaccine should be considered in Croatia due to the severe clinical course and outcome of IMD.

### Abbreviations:

- ABM - acute bacterial meningitis
- AOM - acute otitis media
- Hi - Haemophilus influenzae
- Hib - Haemophilus influenzae type b
- IBD - invasive bacterial disease
- IHD - invasive H. influenzae disease
- IMD - invasive meningococcal disease
- IPD - invasive pneumococcal disease
- MCC - meningococcal serogroup C conjugate vaccine
- NIP - national immunization program

NTHi - nontypeable *Haemophilus influenzae*  
 OB - occult bacteremia  
 PPV23 - pneumococcal 23-valent polysaccharide vaccine  
 UK - United Kingdom

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#### SUKOB INTERESA/CONFLICT OF INTEREST

Autori su popunili *the Unified Competing Interest form na www.icmje.org/coi\_disclosure.pdf (dostupno na zahtjev)* obrazac i izjavljuju: nemaju potporu niti jedne organizacije za objavljeni rad; nemaju financijsku potporu niti jedne organizacije koja bi mogla imati interes za objavu ovog rada u posljednje 3 godine; nemaju drugih veza ili aktivnosti koje bi mogle utjecati na objavljeni rad./ *All authors have completed the Unified Competing Interest form at www.icmje.org/coi\_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.*

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### Sažetak

#### EPIDEMIOLOGIJA INVAZIVNIH BAKTERIJSKIH BOLESTI U DJECE U HRVATSKOJ PRIJE I NAKON UVOĐENJA CIJEPLJENJA PROTIV HAEMOPHILUS INFLUENZAE TIP A B

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**Uvod:** *Haemophilus influenzae* tip b, *Streptococcus pneumoniae* i *Neisseria meningitidis* su prije uvođenja konjugiranog Hib cjepiva bili vodeći uzročnici invazivnih bakterijskih bolesti (IBB) u djece mlađe od 5 godina. U zemljama koje su uvele rutinsko cijepljenje konjugiranim Hib cjepivom došlo je do značajnog pada incidencije, a gotovo i nestanka invazivne *Haemophilus influenzae* bolesti (IHB).

**Cilj:** Prikazati učestalost i karakteristike IBB u djece i adolescenata mlađih od 18 godina prije i nakon uvođenja konjugiranog Hib cjepiva u hrvatski nacionalni imunizacijski program (NIP) 2002. godine.

**Ispitanici i metode:** Retrospektivna analiza elektronskih i arhivskih podataka bolesnika u dobi od 0 do 18 godina s etiološki dokazanom IBB liječenih u Klinici za infektivne bolesti "Dr. Fran Mihaljević" (KIB FM) u razdoblju od 1997. do 2014. godine.

**Rezultati:** Obuhvaćeno je 1.112 bolesnika koji su podijeljeni u tri razdoblja: prvo (referentno) razdoblje prije uvođenja Hib cjepiva te u dva postvakcinalna razdoblja. Do statistički značajne promjene udjela u drugom razdoblju došlo je za meningokok ( $p < 0,05$ ), BHSB ( $p < 0,05$ ) i *Haemophilus influenzae* ( $p < 0,0001$ ), a taj se trend održao i u trećem razdoblju za *Haemophilus influenzae* ( $p < 0,0001$ ). Također, bilježi se pad u broju slučajeva Hib meningitisa ( $p < 0,0001$ ).

**Zaključak:** Uvođenje Hib cjepiva u hrvatski NIP dovelo je do značajnog smanjenja incidencije IHB. *Streptococcus pneumoniae* i *Neisseria meningitidis* i dalje su vodeći uzročnici IBB stoga valja razmatrati uvođenje adekvatnog pneumokoknog i meningokoknog cjepiva u hrvatski NIP.

Deskriptori: CIJEPLJENJE, DJECA, HAEMOPHILUS INFLUENZAE TIP B, INVAZIVNE BAKTERIJSKE BOLESTI, NEISSERIA MENINGITIDIS, STREPTOCOCCUS PNEUMONIAE

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