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Original article

Serotype changes and antimicrobial nonsusceptibility rates of invasive and non-invasive *Streptococcus pneumoniae* isolates after implementation of 10-valent pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) in Bulgaria

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ABSTRACT

The 10-valent pneumococcal conjugate vaccine (PCV10) has been included in Bulgarian Childhood Immunization Program since 2010. This study aimed to assess serotype distribution and antimicrobial resistance of 198 invasive and non-invasive *Streptococcus pneumoniae* strains that had been isolated in Bulgaria during 2011–2016 from patients with invasive (IPD) and non-invasive (NIPD) pneumococcal diseases. The most common invasive serotypes were 3 (10.1%), 19F (4.0%), and 7F (3.0%). A significant decrease in the proportion of invasive vaccine types (VTs) from 64.2% to 35.2% was found in comparison with pre-vaccine era. The most common serotypes among middle ear fluids were 3, 19A and 19F (5.6% each), and VTs fell down from 66.4% to 40.0% in post-PCV10 period. Among respiratory isolates, the most prevalent serotypes were some emergent serotypes such as 15A/B/C (5.0%), 19A, and 6C (4.0% each). VTs decreased significantly (16.3%) among vaccinated children compared to unvaccinated children and adults (44.0%). Two non-VTs (19A and 6C) have increased significantly more ($p < 0.05$) in vaccinated children than in unvaccinated patients. The rates of antibiotic nonsusceptible *S. pneumoniae* in Bulgaria remained high in post-PCV10 era.

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Among all source of isolates, antimicrobial nonsusceptibility rates were: oral penicillin – 46.5%, trimethoprim-sulfamethoxazole – 45.4%, erythromycin – 43.9%, tetracycline – 37.4%, and multidrug-resistance (MDR) was 44%. The most common MDR serotypes were 19F, 19A, 6A/C, 15A/B/C and 23A. Our results proved that PCV10 vaccination substantially reduced VTs pneumococcal IPD and NIPD. There has been a shift in the distribution of *S. pneumoniae* serotypes mostly in vaccinated children but also in the whole population and strong serotype-specific antibiotic resistance was observed after vaccine implementation. Therefore, it is important to continue monitoring serotype changes and pneumococcal resistance among all patient ages in addition to aid in determining the long-term effectiveness of PCV10 interventions.

Introduction

Despite the development of antipneumococcal vaccines *Streptococcus pneumoniae* is still an important cause of severe invasive pneumococcal diseases (IPD) worldwide. Pneumococcus is also a global cause of less serious but more frequent respiratory tract infections, such as otitis media, sinusitis, and non-bacteremic pneumonia.[1] The prevention of pneumococcal disease is hampered by antigenic diversity of the pneumococcal capsule, a major virulence factor of this species and a target of all current commercially available vaccines.[2] There are at least 95 capsule types (serotypes) that differ by invasiveness, disease severity, antibiotic resistance profiles, and case fatality ratio.[2] Since the currently available vaccines provide protection only against a limited number of serotypes their distribution and characteristics warrant careful continuous monitoring.

The first, heptavalent pneumococcal conjugate vaccine (PCV7), targeting seven serotypes of *S. pneumoniae* (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) has been available for infant vaccination programs in the United States since the 2000s, subsequently in European and other countries.[2] Following the introduction of PCV7 vaccination there has been a reduction of IPD caused by serotypes included in the vaccine among the adult population (indirect or herd effects) which has been attributed to a reduction of nasopharyngeal colonization in vaccinated children.[3] Furthermore, as serotypes included in the PCV7 were those which expressed the highest rates of antibiotic resistance, PCV7 vaccination had a concomitant decreasing effect on the incidence of IPD and other non-invasive pneumococcal diseases (NIPD) caused by antibiotic-resistant *S. pneumoniae*.[4] However, after the introduction of PCV7 the incidence of pneumococcal diseases caused by non-PCV7 serotypes such as 1, 3, 6A, 6C, 7F, and 19A increased in countries with routine vaccination.[5] Vaccine serotypes (VTs) have nearly disappeared and have been largely replaced by non-vaccine serotypes (NVTs).[6] PCV7 programs have not been affected because the increases in incidence of NVTs infections are small compared with the decreases in incidence of IPD caused by VTs.[5]

Since 2010, two broad spectrum PCVs, the 10-valent (PCV10) and 13-valent (PCV13) are available and both vaccines proved to be more effective than PCV7.[7] The 10-valent pneumococcal nontypeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV or PCV10) contains the PCV7 serotypes, as well as serotypes 1, 5, and 7F. As has been shown, PCV10 has greatly reduced VTs IPD and provides indirect protective effects via reduced VTs carriage.[8–11] Additionally, the PHiD-CV vaccine has showed significant protection against NTHi otitis media.[12]

In April 2010, the Bulgarian Immunization Program introduced PCV10 as a first PCV for universal childhood vaccination of all infants in a three-dose schedule at 2, 3, and 4 months of age with a booster at 12 months (3 + 1 schedule). PCV10 vaccination of targeted age-groups is very high (>90%) according to the national epidemiological data (National Center of Health Information). Prior to PCV10 implementation, PCV7 had not been used in our country despite being available in the market since 2008.

The main goal of this study was to provide an inventory of *S. pneumoniae* strains which were responsible for invasive and non-invasive infections in children and adults in the era of PCV10 vaccination. The objectives were to determine whether the use of PCV10 caused a shift in the pnemococcal serotype distribution and serotype relationship to antibiotic-resistance patterns in order to evaluate the impact of the vaccine in our country where mass vaccination of infants has been implemented.

Material and methods

Patients and specimen collection

This post-PCV10 surveillance study was conducted in a total of 198 non-duplicated *S. pneumoniae* strains collected between May 2011 and May 2016 at several clinical microbiological laboratories throughout Bulgaria. The study has been initiated one year after PCV10 introduction into our routine vaccination schedule. Our Department of Medical Microbiology received these isolates from three laboratories located in Sofia and another three hospital laboratories located elsewhere in the country (Medical Universities of Plovdiv, Pleven, and Varna) on a voluntary basis. Clinical and demographic data (date of birth or age, date of admission in hospital, diagnosis) were collected by review of the medical charts or from the data recorded on the request of cultures to laboratories. The pneumococcal strains were isolated from invasive and non-invasive