

# PNEUMOCOCCAL CARRIAGE IN HEALTHY CHILDREN AS AN INDICATOR OF THE EVOLUTION OF THESE PATHOGENS ON THE BACKGROUND OF THE USE OF PNEUMOCOCCAL CONJUGATE VACCINES

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## Abstract

**Introduction.** The use of pneumococcal conjugate vaccines (PCVs) began globally in the early 2000s, with many countries incorporating them into national immunization programs. PCVs proved to be effective against those serotypes of the pneumococci (*S. pneumoniae*, *Spn*) that were part of the vaccines, leading to declines in invasive pneumococcal disease (IPD) and reduced *Spn* circulation among healthy individuals for the first years after vaccination implementation.

**Aim.** To analyze the characteristics of *Spn* circulation against the background of widespread PCV use, subsequent trends in serotype changes, and vaccine effectiveness (VE) in order to optimize its strategy.

**Materials and methods.** This retrospective epidemiological review used systematic analysis of literature from 2010-2020s to examine global trends in IPDs, *Spn* carriage, serotype distribution, VE, and the emergence of new dominant serotypes before and after PCV introduction.

**Results.** The analysis of the global situation demonstrates the dynamics of changes in *Spn* carriage among healthy children, the evolution of *Spn* serotypes under vaccine pressure, a gradual decline in VE, and a continuous increase in the valency of PCVs in use. Data from Ukraine are presented, where PCVs are not included in the national immunization program; nevertheless, over the past 10 years, a sharp decline in *Spn* carriage (~6.6-fold) has also been observed, along with a reduction in the number of circulating *Spn* serotypes. In particular, no circulation of PCV13 vaccine serotypes 3, 5, 14, and 19A was detected, nor of serotype 6C, which is antigenically related to the vaccine serotype 6A. Meanwhile, non-encapsulated *Spn*, now recognized as IPD etiological agents, in the children's nasopharynx increased 4.5-fold, highlighting the need to consider both encapsulated and non-encapsulated *Spn* in predicting future VE.

**Conclusions.** Given the high effectiveness of PCVs only against vaccine serotypes, in countries with moderate *Spn* circulation the most optimal strategy is vaccination of medical, age-related, and epidemic risk groups using the highest-valency PCVs. In addition to protecting these risk groups against vaccine serotypes, this approach may help limit their replacement by other *Spn* serotypes.

**Keywords:** pneumococci, non-capsular pneumococci, pneumococcal carriage, invasive pneumococcal diseases, pneumococcal conjugate vaccines

## INTRODUCTION

The long-term use of pneumococcal conjugate vaccines (PCVs) worldwide within immunization programs has not diminished the relevance of invasive pneumococcal diseases (IPDs). The first to be introduced was the 7-valent PCV (PCV7, 2000), followed by PCV10, PCV13, PCV20, and most recently, PCV21 (2024) [1, 2]. The serotype composition of these vaccines has been

described previously [2]. However, widespread PCV implementation, so extensive that some researchers have called the 21st century the «era of pneumococcal vaccines», has not enabled substantial progress toward effective IPD control. In the European Union/European Economic Area EU/EEA, where PCVs have been widely used for over two decades, 17,700 IPD cases were reported in 2022 (5.1 per 100,000), comparable to pre-COVID-19 levels. The highest incidence was among infants under 1

year and adults over 65 (13.4 and 12.6 per 100,000) [3]. Under vaccine pressure, *Streptococcus pneumoniae* (*Spn*) serotypes included in PCVs (vaccine serotypes, VSTs) are displaced and replaced by previously less prevalent non-vaccine serotypes (NSTs). Colonization of the nasopharynx may lead to pneumonia, meningitis, otitis media, or other conditions, though infection often results only in carriage. The risk of disease is higher in young children, older adults, individuals with comorbidities, and immunocompromised persons. Monitoring *Spn* carriage in healthy children allows assessment of its intensity and identification of dominant serotypes, which is essential for evaluating vaccine effectiveness (VE), understanding pathogen dynamics, forecasting epidemic trends, and guiding preventive measures.

### AIM

The aim of this study is to analyze the characteristics of *Spn* circulation against the backdrop of widespread PCV use, to identify further trends in serotype dynamics, and to assess VE in order to optimize vaccination strategies.

### MATERIALS AND METHODS

The study is a retrospective epidemiological and analytical review. A systematic search of the literature was conducted in the international databases PubMed, Scopus, and Web of Science, as well as on the official websites of the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the European Centre for Disease Prevention and Control (ECDC). Using content analysis, publications were selected according to predefined thematic areas, including trends in invasive pneumococcal disease during the 2010s-2020s, considering regional and age-specific differences before and after the introduction of PCVs; carriage and persistence of *Spn*; serotype distribution; VE; circulation of serotypes in the pre- and post-PCV periods; and the emergence of new dominant serotypes, followed by comparison and critical appraisal of the data.

### RESULTS

***Assessment of the current situation of pneumococcal infections in the world.*** An example of changes against the backdrop of over 20 years of PCV use in most countries is the impact of vaccination on the distribution of VSTs and their role in IPDs. In a WHO project, surveillance data from 41 countries with PCV10 or PCV13 coverage of at least 70% were evaluated. Among children under 5 years, the most frequent causes of IPDs were VSTs 19A, 3, and 14. Other VSTs were detected rarely, confirming the VE against all other VSTs [4]. In the EU/EEA in 2022, only 46% of serotyped isolates from children under 5 years belonged to PCV13 VSTs. Among the five prevailing serotypes in children

up to 14 years, only two were VSTs – 3 and 19A [3]. The characteristics of *Spn* of these two serotypes, which distinguish them from others and reduce VE, we described earlier [2]. These were not relevant in the pre-vaccine period but began to prevail after widespread use of PCV7. Currently, new serotypes 8, 10A, and 24F with pronounced invasiveness have also emerged in Europe. Comparing these data with those from the 41 countries mentioned above, the predominance of VSTs 3 and 19A appears to be a global trend, largely unaffected by immunization. In a study of antimicrobial resistance (AMR) of *Spn* isolates from IPD patients in EU/EEA in 2022, 19.0% were resistant to erythromycin and 9.9% to cephalosporins [3]. Thus, vaccination has not led to the elimination of AMR.

Based on approximate calculations for 180 countries for the period 2015-2045, global use of PCV13 (at the current coverage level of the three-dose pertussis-diphtheria-tetanus vaccine) could annually prevent 0.399 million child deaths and 54.6 million cases of IPDs. The largest number of IPD cases is expected in the African and Asian regions (399,000 and 275,000, respectively, compared to 7,540 in North America and 4,860 in Europe) [5, 6]. We would agree with these estimates if IPD incidence were consistently determined by the same factors, in particular if its pathogens did not have a large number of serotypes and the capacity for accelerated evolution under the «immune pressure» of PCVs. There are also serious doubts about achieving PCV coverage at the level of the pertussis-diphtheria-tetanus vaccine. Therefore, these estimates can be considered only as theoretical, and the stated goal remains, for now, unrealistic.

***Pneumococcal carriage, influencing factors, and detection approaches.*** The persistence of *Spn* in healthy individuals sustains the ongoing epidemiology of pneumococcal infections, as carriers directly contribute to its circulation and can transmit the pathogen. Carriage rates, disease incidence, and serotype distribution vary across regions due to multiple factors. Therefore, beyond general discussions of *Spn* carriage in healthy populations, it is crucial to examine its epidemiological characteristics within specific countries and regions to understand local dynamics and risks.

Individuals vary considerably in their susceptibility to respiratory pathogens and in clinical outcomes, due to multiple factors. Beyond pathogen virulence, immune status, host genetics, and environmental influences, the commensal microbiota, the human microbiome, plays an important role and may include potential pathogens such as *Spn*. These complex, niche-specific bacterial communities vary with localization, host condition, and factors like age, season, feeding practices, and viral presence. Correlations exist between microbiota composition, its stability, and susceptibility to respiratory

infections. Within respiratory bacterial communities, streptococci are central [7]. These interactions and their implications for vaccination require further study.

Another study showed that a more diverse microbiome and low abundance of *Corynebacterium* spp. before infection were associated with *Spn* persistence [8]. In young children, *Spn* detection varied by serotype, from 6-7% for 6A and 35A/B to 20% for 6B and 23A/B. Its presence was influenced by *Dolosigranulum*, *Corynebacterium*, *Staphylococcus*, *Haemophilus*, *Moraxella*, non-pneumococcal streptococci, *Gemella*, *Prevotella*, and *Fusobacterium*, suggesting co-colonization affects microbiota composition depending on serotype phenotypes [9]. Factors promoting carriage include young age, ethnicity, respiratory symptoms, daycare attendance, living with young children, poverty, smoke exposure, seasonality, co-colonization, breastfeeding, and antibiotic use. Average carriage rates varied by income, from 51% in low-income settings to 28.5% in high-income settings [10].

The WHO working group study found that a diverse microbiome and low *Corynebacterium* spp. abundance before infection were linked to *Spn* persistence [8]. In young children, detection varied by serotype (6-7% for 6A/35A/B; 20% for 6B/23A/B) and was influenced by co-colonizing bacteria [9].

**Levels, serotypes, and other characteristics of pneumococcal circulation among healthy individuals.** Carriage rates of *Spn* in healthy populations vary geographically and depend on the cohorts under study. For example, in closed settings they are consistently higher, as such environments intensify the activity of transmission factors. Monitoring carriage makes it possible to determine *Spn* serotypes at the population level and, when PCVs are included in the Immunization Schedule, to assess the impact of vaccination on the prevalence of VSTs, their individual serotypes, and the emerging epidemiological role of NSTs and non-encapsulated *Spn* (NESp).

The introduction of PCVs initially reduced IPD incidence, raising hopes for disease control. However, *Spn* often persists as a predominant nasopharyngeal bacterium in children, detected as frequently as before vaccination [14]. Below, we present data on *Spn* carriage among healthy individuals in selected countries to highlight differences in circulation intensity, serotype diversity, the emergence of new serotypes under vaccine pressure, and the gradual decline in vaccine effectiveness, which drives the development and use of higher-valency vaccines.

In **Poland**, during the PCV use (2016-2020), *Spn* was detected in 40.1% of unvaccinated children under 5 years of age; in 25.3% of cases, multiple serotypes were identified simultaneously. The risk of carriage was significantly higher among children attending

preschool institutions and during the autumn-winter months. The most prevalent serotypes were 23A, 6B, 15BC, 10A, and 11A. VSTs after PCV10 and PCV13 were 23.2% and 26.3%, respectively [15]. In **Finland**, PCV10 use, which includes protein D of non-typeable *H. influenzae*, reduced VST carriage and showed trends toward lower overall *Spn* carriage, mainly VSTs 6B, 14, 19F, and 23F, along with a decline in NST 19A and a slight later increase in VSTs [16]. This raised questions, particularly about the reduction of 19A in vaccinated children aged 18-22 months, as PCV10 does not target it [17]. Each study continues to highlight areas needing further investigation. In **England**, where PCV7 has been used since 2006 and PCV13 since 2010, no significant reduction in *Spn* carriage among children under 5 years of age was observed in 2012-2013 compared with the pre-vaccination period. The carriage rate was 47.7%, versus 51% in 2008-2009 and 48.4% in 2001-2002. The predominant serotypes were VSTs included in PCV13 (7F, 19A, 3) and NSTs (8, 33F) [18]. The introduction of PCV10 in 2019 in **Croatia** was accompanied by an increase in *Spn* carriage from 19.9% to 28.7%, mainly due to NSTs (6C, 11A, 19A, 23A) [19]. In **Greece**, among kindergarten children (96.6% with  $\geq 1$  PCV7 dose), *Spn* was detected at least once in 78.5% across four exams. Serotype 19A was frequent (17.1%), while NSTs made up 73.1% of isolates. Other common serotypes included 23B, 15B/C, 16F, 21, 11A, 15A, 6C, 10A, 22F, and 23A, with NSTs 21 and 16F persisting 5-14 weeks [20]. In similar studies from **Portugal**, after PCV13 introduction, *Spn* carriage among kindergarten children  $\leq 6$  years remained high (60.2%), with VSTs at 10.7% versus 47.6% pre-vaccination. The most common VSTs – 19F, 3, and 19A – showed a downward trend, notably serotype 3, which has low VE. Prevalent NSTs included 15B/C, 11A, 23B, 23A, and NESs (51.9%). Penicillin and macrolide resistance increased, driven by NSTs. Genomic lineages traditionally linked to VSTs (CC156-GPSC6, CC193-GPSC11) were now mainly among NSTs, indicating *Spn* adaptation to vaccination and antimicrobial pressure. These findings call for balanced, evidence-based strategies for future prevention [21]. In **Turkey**, PCV7 was introduced in 2008 and PCV13 in 2011. In 2014, the *Spn* carriage among children aged 0-13 years was 9.8%, with vaccination coverage at 56.6%. Of the isolates, 53% belonged to VSTs and 12.2% to NESp. The most common serotypes were 3, 19F, 6A/B, 11A, and 15B [22]. Among vaccinated children under 5 years (2019-2020), carriage increased to 17.8%. The most prevalent serotypes were 15B, 23F, 23A, 11A, 19F, and 15F. Overall, 27.2% of *Spn* isolates were classified as VSTs [23]. During the COVID-19 pandemic (2022), *Spn* carriage among individuals 0-24 years was 19.6%, with no substantial differences across age groups (15.6-20.7%). Vaccination coverage was  $\geq 82\%$  among those under 15 years of age. Vaccination was associated with significantly lower carriage only in children  $\leq 10$  years old (17.8-19.7%). A total of 27 *Spn* serotypes

were identified, with VSTs accounting for 77.3%. The dominant serotypes were 19F, 6A/B, 3, 23F, and 15B/C [24].

In the **United States**, PCV7 (2000) and PCV13 (2010) gradually shifted *Spn* serotype distribution, reducing VSTs among healthy children to 3% and increasing NSTs to 97%. Unlike many countries, AMR initially declined [25, 26]. After PCV13, NST 35B became predominant with low AMR, but several years later resistance rose sharply (2.9% → 27.9%) due to the ST156 lineage. Capsular switching between multidrug-resistant VSTs (e.g., 9V, 14, 19A) and 35B illustrates *Spn*'s evolutionary adaptation under vaccine pressure

Differences in nasopharyngeal *Spn* colonization among Indigenous and non-Indigenous children in **Australia** were observed before and after three doses of PCV7. Carriage prevalence was 19% and 16%, while NSTs accounted for 22% and 7%, respectively. Vaccinated Indigenous children had lower VSTs and higher NSTs carriage than unvaccinated peers; no similar pattern occurred in non-Indigenous children. AMR profiles also differed: 30-43% of NESp isolates showed resistance to two or three antibiotics [28]. It may be assumed that *Spn* carriage was likely influenced by both genetic susceptibility and living conditions. Later, following the PCV13, *Spn* carriage among Indigenous children under 5 years declined (72.2% → 66.8%), while it slightly increased in ages 5-14 (49.4% → 53.2%). The most prevalent serotypes became 11A, 15B, 16F, and 19F. Complete resistance to penicillin was detected among *Spn* serotypes 19A, 19F, and NESp isolates [29]. The rapid emergence of AMR, including in newly prevalent serotypes, likely reflects widespread antibiotic use in this population.

In Asian countries as well, the introduction of vaccination has not had a substantial impact on *Spn* carriage. The introduction of PCV10 in **Pakistan** (2013) was preceded by a study of *Spn* carriage in different areas in children, which was 73.6-79.5% in infants and 78.2% in children aged 12-59 months. Between 30.7% and 38.9% of *Spn* belonged to VSTs. The most common serotypes were 6A, 23F, 19A, 6B, and 19F. Thus, at the time of vaccine introduction, approximately three out of four children were colonized with *Spn*, and this rate was similar across comparable age groups in different communities. Subsequent observations in these communities demonstrated changes in VST carriage associated with PCV10 use [30]. During 2014-2018, *Spn* carriage in children under 2 reached 75%, above pre-vaccination levels; VSTs accounted for 16% and NSTs 84%. Serotypes 6B, 9V/9A, and 19F declined over twofold, while NSTs 19A, 21, and 10A increased 33-70%. VE was shown for 9V/9A, 19F, and 6A [31]. After PCV10 was replaced with PCV13 in 2021, 2022 carriage remained 70% (60.1% coverage). PCV10 VSTs dropped from 13.2% to 7.2%, additional PCV13 VSTs from 18.5% to 11.4%, and

NSTs rose from 68.3% to 81.4%, with projected AMR of 46-88.5% [32]. Overall, no sustained VE was observed. In **Indonesia** (2017), *Spn* carriage was 30.9% in urban areas and 87.6% in rural areas, with PCV13 VSTs at 15.0% and 52.6%, respectively. The most common VSTs were 6B, 19F, and 3 in urban areas, and 6B, 19F, and 23F in rural areas. A total of 61.5% of isolates showed AMR to ≥ 1 antibiotic, 13.2% to ≥ 3 classes; among VSTs, 73.9% were resistant and 19.9% showed multi-drug resistant [33]. These results indicate very low VE, especially in rural settings, and high AMR among VSTs. Similar to Pakistan, carriage intensity and dominant serotypes differed between urban and rural areas, showing substantial regional epidemiological variability.

In several regions of **China**, between 2016 and 2023, carriage of PCV13 VSTs was studied in unvaccinated children aged 2 months to 5 years, assessed by serotype-specific IgG levels (>0.35 µg/mL). Carriage rates were higher for 6B, 14, 19A, and 19F, with the lowest values observed in the 7-11-month age group [34]. These findings correlate with the predominant serotypes causing IPDs in the country. In **Hong Kong**, during 2013-2014, *Spn* carriage among children aged 2-18 months was only 5.5%. The predominant serotypes were 15 (15B/C, 15A/F) and 23A. VSTs after PCV7 accounted for 2.4%, PCV13 VSTs for 10.7%, and NSTs for 89.3% of isolates. The proportion of isolates exhibiting AMR ranged from 7.3% to 79.3% [35]. In **South Korea**, PCV10 and PCV13 were introduced in 2010. In 2014, among children 6-71 months, NSTs accounted for 88.3% of isolates, mainly 23A, 15B, and 15C, with highest carriage in the youngest children. AMR was 86% to penicillin, 90.5% to erythromycin, and 81.5% showed multidrug resistance; NSTs showed 89% penicillin resistance [36]. Despite vaccination, *Spn* carriage remains high, dominated by AMR NSTs. From 2014-2019, PCV13-vaccinated children showed age-related increases in carriage more markedly than PCV10 recipients [37].

*Spn* carriage in the African region also exhibits country-specific differences in trends and characteristics, even with the use of the same vaccines. In **Kenya**, 1-2 years after the introduction of PCV10 in 2011, *Spn* carriage levels remained stable, with a reduction in VSTs. By 2017, with coverage of three doses exceeding 90% among children under 5 years in two communities, carriage ranged from 59.1% to 83.3%, compared with 85.7%–92.9% in 2013. In 2019, VSTs were detected in 9.1%–13.9% of participants, compared with 13.3%–17.3% in 2013. Predominant serotypes included NSTs 3, 6A, 19A, 35B, and VST 19F. Later, Kenya switched to a different PCV10 that also included serotypes 6A and 19A [38]. These data indicate an extremely low VE of PCV10. In **Mozambique**, PCV10 was introduced in 2013 and replaced with PCV13 in 2017-2019. Among children under 5 years, PCV13 VST carriage was 80.7%; among those aged 5-18 years, 7.8%; and in

adults  $\geq 18$  years, 35.4%. The most frequently detected VSTs were 19A and 6A. Carriage among children under 5 remained stable at around 80%; carriage of PCV10 VSTs decreased from 17.7% to 10.1% [39]. Thus, in this country as well, no expected VE in overall *Spn* circulation was observed, although the proportion of VSTs declined.

Among schoolchildren aged 7-17 years in **Ethiopia** (2022-2023), *Spn* carriage was 16%, with the highest rates observed among students aged 11-14 years (66.7%). Vaccination coverage was 92.9%. *Spn* isolates exhibited higher AMR to tetracycline (42.6%) and trimethoprim-sulfamethoxazole (33.3%) [40]. Compared with other African countries, *Spn* carriage among children was significantly lower, although the highest rates were observed not in the youngest age group, but among school-aged children. In **Gambia**, PCV7 was introduced in 2011 and PCV13 in 2013. Post-vaccination studies tracked changes in *Spn* serotypes by age and time since vaccination. Among infants receiving three doses, overall carriage was 85.4%. VST carriage decreased after PCV13 (4.9% vs. 9.4% for PCV7; 18.3% vs. 33.3% for PCV13). Serotypes 6A (15.3%  $\rightarrow$  5.7%) and 19F (5.6%  $\rightarrow$  1.7%) declined, while NESp increased (0.3%  $\rightarrow$  6.0%), most originating from previously typeable serotypes losing capsule expression [41]. Over time, VSTs in infants fell (33.3%  $\rightarrow$  11.4%), NSTs rose (53.1%  $\rightarrow$  74.4%), with 7F and 16 predominating among VSTs and NSTs, respectively. VSTs more often lost capsule expression [42]. In 2022, overall carriage was 32.1%, with VSTs at 6.4%, highest in children 5-9 years (13.6%). Among fully vaccinated children, VST carriage was 1.6 times higher than in infants 0-11 months, and similar between vaccinated and unvaccinated children under 10. The most common serotypes were 19F, 3, and 6A. Ten years post-PCV13, residual VST carriage persists, especially in older children [43]. Another study suggested a PCV13 booster before school, as 5-14-year-olds contribute  $\sim$ 63% of VST transmission, indicating gradual decline in post-vaccination protection with age [44]. In **Malawi**, PCV13 was introduced in 2011. Pre-vaccination (2009-2011) VST prevalence rates were 11.4%, 45.1%, 28.2%, 21.2%, and 6.6% among children aged 6 weeks, 18 weeks, 1-4 years, 5-15 years, and their mothers, respectively. In the post-vaccination period (2014), this indicator decreased in almost all groups, except for unvaccinated 6-week-old infants and children aged 1-4 years. Carriage of NSTs increased only among vaccinated children aged 1-4 years [45]. No significant impact of vaccination on the displacement of VSTs from circulation was observed, similar to findings in other African countries. A similar situation was in **Cameroon**, with PCV13 introduction in 2011: among vaccinated children aged 24-36 months (2015), *Spn* carriage prevalence was 61.8%, including 18.0% VSTs. Eleven of the 13 VSTs were identified, with predominance of 19F and 15B/C. Thus, four years after vaccine introduction, almost all VSTs continued to circulate [46].

**Ukraine.** Among the countries we analyzed, Ukraine is the only one in which PCV has not been included in the routine immunization schedule. Therefore, assessing the dynamics of *Spn* carriage prevalence and serotype distribution against the background of very limited PCV use (only as a recommended vaccine) is of interest from the perspective of the natural evolution of the IPD epidemic process and the development of optimal strategies for its control. The first studies in Ukraine were conducted in 2013-2014 [47-51], and the most recent in 2021-2025 [52]. In earlier studies, overall *Spn* carriage among children aged 6 months-5 years ranged from 50.4% to 53.8%, varying by group: 95.6% in orphanages, 60.4-60.9% in organized groups, and 37.3-42.1% in unorganized children. Although orphanage residents comprised only 6.8-7.5% of those examined, they accounted for 22% of isolates, markedly increasing overall carriage. Identified serotypes included 3, 4, 5, 6A/B, 6C, 7A/F, 9V, 14, 18C, 19A, 19F, 20, and 23F. NESp represented 11.1%, and 33% were non-typeable (44.1% total). While 97.3% of typed serotypes were covered by PCV13, VSTs comprised only 46.3% of all isolates, and even less excluding orphanages. These findings support vaccinating children in closed institutions and assessing microbiome shifts and invasive potential under vaccine pressure.

In a recent study involving children aged 6 months to 5 years, *Spn* was detected in the nasopharynx in 7.6% of cases (ranging from 3.2% to 18% by study year). Of these isolates, 51% were encapsulated, while 49% were NESp. The following serotypes were identified: 4, 6A/B, 7A/7F, 9V, 11A/D, 18, 19F, and 23F, with predominance of 6A/B, 19F, 23F, and 18; 65.5% of the serotypes belonged to PCV13 VSTs [52].

## DISCUSSION

Summarizing the above data, the presented findings indicate the high effectiveness of PCVs used worldwide against VSTs in countries with temperate climates. The lowest effectiveness was observed for *Spn* serotypes 3 and 19A, which is associated with their biological characteristics [2]. It should be noted that the impact of vaccination on *Spn* carriage among healthy individuals was most pronounced in the first years following vaccine introduction [21, 27, 31, 32]. Subsequently, VE declined due to replacement of VSTs by newly emerging and epidemiologically relevant serotypes, the appearance of additional serotypes, increased circulation of NESp, and the acquisition of invasive properties by these strains [21, 27, 31, 32]. In some settings, *Spn* carriage rates even increased in the context of vaccination [23, 24]. Across different regions, these changes were accompanied by varying degrees of AMR, with a tendency toward increase driven by both NSTs and NESp, as well as differences in the circulating VST and NST serotypes and in the proportion of

NESp [21, 27, 28, 29, 35, 36, 37, 46]. In certain countries, restoration of VST carriage has been observed as previously vaccinated children grow older, indicating waning VE over time [43, 44]. These findings underscore the need for an individualized approach to selecting vaccination strategies at the national level. The highest carriage rates among healthy individuals, despite widespread vaccination and continued circulation of VSTs and NSTs, have been reported in Asian and African countries [33, 37, 38, 39, 41, 46].

When comparing the results of the above-mentioned studies conducted in Ukraine over time [47-52], it should be noted that, in the absence of vaccine implementation, a substantial decline in *Spn* carriage occurred (approximately 6.6-fold overall, 6-fold among children in organized groups, and 4-7.7-fold among non-organized children). The number of circulating *Spn* serotypes also decreased. In particular, circulation of such PCV13 VSTs as 3, 5, 14, and 19A was no longer detected, nor was serotype 6C, which is antigenically related to VST 6A. That is, this positive change is not the result of the introduction of PCVs. We do not agree with the author's statement [52] that IPDs (meningitis, sepsis, pneumonia with bacteremia) are vaccine-preventable diseases that can be averted by vaccination of the respective age groups. This would be possible only if IPDs were caused exclusively by *Spn* serotypes included in PCVs. As demonstrated above, *Spn* undergoes continuous evolution, and increasing vaccine valency cannot halt this natural process aimed at preserving the microorganism as a species.

Taking into account the results of the analysis of *Spn* carriage in different countries worldwide, particularly its direct association with the risk of IPDs; the continuous shift of leading serotypes under vaccine pressure, which prompts an arguably ineffective expansion of PCV valency through inclusion of antigens of newly emerging serotypes; the marked decline in *Spn* carriage among children in Ukraine in the absence of routine vaccination; and the substantial increase in the proportion of NESp (49%) among them, against which vaccination is ineffective, we consider it appropriate for Ukraine to recommend PCVs only for high-risk groups, using vaccines with the highest available valency, as the most effective and economically justified strategy for the prevention of IPDs in the country.

## CONCLUSIONS

Based on our analysis of *Spn* circulation among healthy individuals against the background of PCV use in national immunization schedules in different countries in dynamics, it should be emphasized that the impact of vaccination on *Spn* carriage was most pronounced in the first years following PCV introduction. Subsequently, effectiveness declined due to replacement of VSTs by newly emerging and epidemiologically relevant serotypes, as well as increased circulation of NESp with acquisition

of invasive properties. Across different regions, these changes were accompanied by varying degrees of AMR *Spn*, with a tendency toward its increase driven by NSTs and NESp, along with differences in circulating VST and NST serotypes and a growing proportion of NESp. This necessitates reconsideration of general recommendations aimed at universal PCV implementation. Each country should conduct an assessment of its epidemiological situation, including the degree of concordance between circulating *Spn* serotypes and the VSTs included in the vaccines planned for use. It is essential to take into account the proportion of NESp among isolates, which significantly affects VE, as well as the anticipated shifts in serotype distribution following vaccine introduction, particularly VST replacement. Therefore, given the high VE limited primarily to VSTs, in our opinion, for countries with moderate *Spn* circulation, the most optimal strategy is vaccination of high-risk groups with PCVs of the highest available valency. This applies to medical, age-related, and epidemiological risk groups. Such an approach would protect those at greatest risk from *Spn*, help restrain rapid shifts in predominant serotypes, and reduce the incidence of IPDs.

**The prospect of further research.** Further research, particularly in Ukraine, should be directed towards the monitoring of IPD with the identification of the leading etiological serotypes of *Spn* and their AMR.

## COMPLIANCE WITH ETHICAL REQUIREMENTS

The conducted systematic review used open public data sources published in peer-reviewed scientific publications, Ukrainian medical journals, and on the official websites (WHO, CDC, ECDC), therefore ethical approval is not required. No element of the work contains plagiarism or fabrication of data. All sources of information are appropriately cited and properly formatted.

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The study did not receive external funding. The authors of the manuscript deliberately declare that there is no actual or potential conflict of interest in the conduct of the research, authorship, and publication of this article.

**Declaration of the use of generative AI in manuscript preparation.** The authors of the manuscript consciously certify that in the process of conducting the research and preparing this manuscript, no artificial intelligence was used for text generation, data analysis, or final editing. All stages of the work were performed exclusively by the authors.

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## Резюме

### НОСІЙСТВО ПНЕВМОКОКІВ У ЗДОРОВИХ ДІТЕЙ ЯК ПОКАЗНИК ЕВОЛЮЦІЇ ЦИХ ПАТОГЕНІВ НА ТЛІ ВИКОРИСТАННЯ ПНЕВМОКОКОВИХ КОН'ЮГОВАНИХ ВАКЦИН

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**Вступ.** Використання пневмококових кон'югованих вакцин (PCV) розпочалося в усьому світі на початку 2000-х років, і багато країн включили їх до національних програм імунізації. PCV виявилися ефективними проти тих серотипів пневмококів (*S. pneumoniae*, *Spn*), які входили до складу вакцин, що призвело до зниження захворюваності на інвазивні пневмококові захворювання (IPD) та інтенсивності циркуляції *Spn* серед здорових осіб протягом перших років після впровадження вакцинації.

**Мета.** Аналіз особливостей циркуляції *Spn* на тлі широкого застосування PCV, подальших тенденцій змін їх серотипів та ефективності вакцинації (ЕВ) для оптимізації її стратегії.

**Матеріали та методи.** У цьому ретроспективному епідеміологічному огляді було використано систематичний аналіз літератури за 2010-2020-ті роки для вивчення глобальних тенденцій IPD, носійства *Spn*, розподілу серотипів *Spn*, ЕВ та появи нових домінуючих серотипів до та після впровадження PCV.

**Результати.** Аналіз глобальної ситуації демонструє динаміку змін носійства *Spn* серед здорових дітей, еволюцію серотипів *Spn* під тиском вакцини, поступове зниження ЕВ та постійне збільшення валентності використовуваних PCV. Представлено дані з України, де PCV не включені до національної програми імунізації; тим не менш, за останні 10 років також спостерігається різке зниження носійства *Spn* (~6,6 рази), та зменшення кількості циркулюючих серотипів *Spn*. Зокрема, не виявлено циркуляції вакцинних серотипів PCV13 3, 5, 14 та 19А, а також серотипу 6С, який антигенно споріднений із вакцинним серотипом 6А. У той же час, кількість некапсульованих *Spn*, які зараз визнані етіологічними агентами IPD, у носоглотці дітей збільшилася в 4,5 рази, що підкреслює необхідність враховувати як інкапсульовані, так і некапсульовані *Spn* при прогнозуванні майбутньої ЕВ.

**Висновки.** Враховуючи високу ефективність PCV лише проти вакцинних серотипів, у країнах з помірною циркуляцією *Spn* найоптимальнішою стратегією є вакцинація медичних, вікових та епідемічних груп ризику з використанням PCV з найвищою валентністю. Окрім захисту цих груп ризику від вакцинних серотипів, цей підхід може допомогти запобігти їх заміні іншими серотипами *Spn*.

**Ключові слова:** пневмококи, некапсульні пневмококи, носійство пневмококів, інвазивні пневмококові хвороби, пневмококові кон'юговані вакцини

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