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REVIEWS

Epidemiology of non-vaccine serotypes of *Streptococcus pneumoniae* before and after universal administration of pneumococcal conjugate vaccines

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ABSTRACT

The universal administration of pneumococcal conjugate vaccines (PCVs) had been demonstrated as an effective way to prevent *Streptococcus pneumoniae* infection. However, the immunity induced by PCVs protected against the infections caused by vaccine serotypes, which were usually more frequent than non-vaccine serotypes (NVTs). The prevalence and pathogenicity of NVTs after universal vaccination have caused widespread concern. We reviewed the epidemiology of non-PCV13 *S. pneumoniae* before and after PCV13 introduction, and explored the potential reasons for the spread of NVTs. Emerging and spreading NVTs can be regarded as the focus for future serotype epidemiological survey and vaccine optimization.

Abbreviations

IPD: invasive pneumococcal disease PCV: pneumococcal conjugate vaccines VT: vaccine serotype
NVT: non-vaccine serotype

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1. Introduction

Streptococcus pneumoniae frequently colonizes the nasopharynx of humans and is transmitted through respiratory droplets. Ninety-two serotypes of *S. pneumoniae* can be identified based on Quellung reaction with polyclonal rabbit anti-sera. Before pneumococcal conjugated vaccines (PCVs) were introduced, serotypes 1, 5, 6A, 6B, 14, 19 F, and 23 F were the common agents that cause invasive pneumococcal diseases (IPDs) globally in children <5 years old[1]. The serotype distribution of pathogenic isolates varied with the time and geographical region of the surveys; the age, infection site, and immunization history of patients; and with the antimicrobial resistance of the isolates.

The World Health Organization (WHO) recommended that all countries should include PCVs in childhood immunization programs as soon as possible. PCV7 (including serotypes 4, 6B, 9 V, 14, 18 C, 19 F, and 23 F) has been widely used and led to a notable incidence decrease of serious infections caused by *S. pneumoniae*. However, the recipient can only obtain immune protection to the seven serotypes included in PCV7. The incidence of infections caused by serotypes not contained in PCV7 (non-PCV7) has increased.[2] In the United States, the colonization of serotypes 3, 19A, 22 F, and 33 F has increased since 2000, when PCV7 was introduced into children's immunization. Particularly, serotype 19A with strong pathogenicity and drug resistance is the attention of caused concern.[3] Similar changes were found in other countries or regions. PCV7 was introduced in Japan in 2010, and the incidence of IPDs in children caused by non-PCV7 serotypes, including 19A, 15A, 15B, 15 C, and 24, has been isolated more frequently since 2012.[4] Eight years after the introduction of PCV7 in Hong Kong, the overall decrease in IPDs was due to the elimination of PCV7 serotypes, whereas an increase in IPDs caused by serotype 3 (non-PCV7) in children >2 years old was monitored.[5] The nasopharyngeal carriage rate of *S. pneumoniae* also dropped, and replacement by non-PCV7 serotypes were likewise observed after PCV7 vaccination.[6] The decrease of VTs accompanied the increase in non-vaccine serotypes (NVTs), which was known as serotype replacement and. The replacement was caused by selective pressure following universal PCV immunization. The increase in NVTs made much concern because some of them may be more aggressive.[7]

In 2010, WHO comprehensively assessed the situation of serotype replacement since PCV7 introduction and decided to use PCV13 (PCV7 plus serotypes 1, 3, 5, 6A, 7 F, and 19A) instead of PCV7.[8] PCV10 (PCV7 plus serotypes 1, 5, and 7 F) was adopted in few countries. Indeed, surveillance data in some developed countries have shown that the introduction of PCV13 in the immunization program was an effective measure in preventing IPDs in children. The disease burden of *S. pneumoniae* has remarkably declined since the promotion and application of PCV13.[9,10] In England and Wales, PCV13 has reduced the overall incidence of IPDs by more than 50%.[11] However, the vaccine has caused a change in the serotype distribution of *S. pneumoniae* apparently. The increased prevalence of NVTs may offset the benefit of the decreased prevalence of vaccine serotypes (VTs) after the introduction of PCV13.[12] Therefore, higher-valent vaccines, including PCV20 (PCV13 plus serotypes 8, 10A, 11A, 12 F, 15B, 22 F, and 33 F), are being developed.[13,14]

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2. Epidemiology of NVTs after the introduction of PCVs

Initially, the impact of PCV vaccination on *S. pneumoniae* serotype distribution has gathered opposing opinions because of remarkable differences indifferent surveillances. Furthermore, the effects of vaccine immunization are very difficult to identify from long-term natural changes in serotype distribution. Recently, more characteristics of NVT isolates were reported. We tried to sort out the epidemiology of NVTs as comprehensively as possible.

2.1 Incidence of IPDs caused by NVTs in the era of PCV13

Immunization benefits are likely to be offset by the prevalence of NVTs in long-term observation, but this event could not be found in a short-term survey. A system review based on 21 surveillance databases found that the overall incidence of IPDs in children in the first year after vaccination was lower (risk ratio [RR] 0.55, 95% confidence interval [CI] 0.46–0.65) than the pre-vaccination period and remained stable for 7 years (RR 0.49, 95% CI 0.35–0.68). Seven years after the introduction of PCVs, the incidence of VT-IPDs decreased each year (RR 0.03; 95% CI, 0.01–0.10), whereas the incidence of NVT-IPDs increased remarkably (RR 2.81, 95% CI 2.12–3.71).[2]

Various national surveys have assessed in detail the changes of IPDs incidence associated with VTs and NVTs. Two years after PCV13 application in Germany, the incidence of IPDs partially rebounded because of the prevalence of non-PCV13 types. Compared with the pre-vaccination period, 63% and 40% reduction in meningitis and non-meningitis IPD rates were recorded in 2012–2013, respectively, but only a 26% reduction in IPD rate was noted in 2015–2016. After the incidence of IPDs achieved the maximum reduction in 2012, the incidence of non-PCV13 IPDs increased sharply in children aged 0–1 year and fluctuated in other age groups. The total incidence of non-PCV13-associated IPDs in children under 16 years of age rose from the lowest point of 1.1/100,000 to 2.5/100,000 in 2015–2016.[15] In Gambia, the incidence of IPD cases caused by PCV13 serotype has decreased by 82% from 78/100,000 to 14/100,000 after the implementation of the PCV13 immunization program since May 2011. Simultaneously, the incidence of NVT-IPDs in children aged 2–23 months increased by 48% from 49/100,000 to 75/100,000. Moreover, a 27% increase in IPD incidence was found in children aged 2–4 years old. Overall, the incidence of NVT-IPDs in children aged 2–59 months has a 47% increase.[16]

Investigations from England and Wales reported changes in incidence and data by age and serotypes. The incidence of non-PCV13 serotypes of all ages increased from 4.19–5.25/100,000, incidence rate ratio [IRR] 1.25, 95% CI 1.17–1.35) in 4 years after PCV13 introduction, because of the increase in a broad range of serotypes in children < 5 years and in adults > 45 years old. The incidence of IPDs caused by non-PCV13 types in children younger than 5 years was higher in 2013–2014 than in 2012–2013 (<2 years: 12.03/100,000–10.83/100,000; 2–4 years: 4.08/100,000–3.63/100,000).[11] If this growth continues, PCV13 immunization for children is likely to have maximum benefit. In England, the incidence of IPDs due to NVTs has doubled (7.97/100,000) since the introduction of PCV7 and accelerated since 2013–2014. The NVTs, especially the serotypes 8, 12 F, and 9 N, were responsible for more than 40% of IPDs in 2016–2017. IPDs incidence in children younger than 5 years remained stable since 2013–2014, but nearly all replacement disease occurred in adults.[17] To summarize intuitively the epidemiological characteristics of serotype distribution after PCV13 vaccination, we list Table 1.

2.2 Proportion of NVTs in *S. pneumoniae* isolates in the era of PCVs

Monitoring the prevalence of pneumococcal disease based on community census is difficult, whereas serotype distribution monitoring based on *S. pneumoniae* isolatesisoaltes is relatively easy. Furthermore, these data can be integrated for regional or global review. Balsells et al.[19] reported that serotype 22 F is the most common NVT (5% of IPD isolates in children), followed by serotypes 12 F, 15 C, 24 F, and 33 F (4% each) according to data from 38 studies (14 countries) where PCV7 was introduced and 20 studies (24 countries) where PCV10/13 have been administered. Overall, after the promotion of PCVs, non-PCV13 serotypes accounted for 42.2% of IPD isolates in children, but differences existed geographically: 57.8% in North America, 71.9% in Europe, 45.9% in the Western Pacific, 28.5% in Latin America, 42.7% in African countries, and 9.2% in Eastern Mediterranean countries.[19]

The common NVTs were different between countries where the same PCVs were administered. Compared with data before PCV13 introduction, a slight increase in non-PCV13 serotype isolates were observed among eight pediatric hospitals in the United States in 2011. The most common NVTs were serotypes 33 F, 22 F, 12, 15B, 15 C, 23A, and 11.[20] In Belgium, the proportion of IPDs caused by non-PCV13 increased from 31% to 49%, which was associated

Table 1. Incidence of IPD caused by NVTs in some studies mentioned above.

		Pre-PCV13 period		Post-PCV13 period		
Country	Age	Year	NVT-associated IPD (/100,000)	Year	NVT-associated IPD (/100,000)	Most prevalent serotypes
England[11]	All	2012–2013	4.19	2013–2014	5.25	-
	<2 years	2012–2013	10.83	2013–2014	12.03	-
	2–4 years	2012–2013	3.63	2013–2014	4.08	-
England[17]	<5 years; >45 years	2013–2014	-	2016–2017	-	8, 12 F, and 9 N
German[15]	<16 years	2012–2013	1.1	2015–2016	2.5	-
Gambia[16]	2–59 months	Before 2011	14	After 2011	78	-
	2–23 months	2010	49	2011	75	-
Israel[18]	All	2009	0.32[a]	2015	0.75[b]	15B/C, 6 C, 23A, 23B, 24 F

[a]Only the incidence of meningitis (not IPD) is included.

with serogroups 12, 8, and 15.[21] In the Balearic Islands, NVT isolates (206/351, 58.7%) increased up to more than half of *S. pneumoniae* isolates in 2016.[22] In Denmark, the majority of IPD cases (71%) in 2014 were caused by NVTs.[23] Seven national surveys from 2007 to 2016 in India found that NVT cases accounted for 21% (281 cases) of IPD cases in children under 5 years of age; the NVTs primarily included types 10 F, 9 N, 11A, 20, and 15B.[24]

NVT-related pneumococcal disease outbreaks could also be associated with age and infection site. The investigation in Denmark found that NVT-IPDs were predominantly found in vaccinated children (91% for 0–4 years). These NVTs were also dominant among the elderly (73% for >65 years).[23] The proportion of NVTs in *S. pneumoniae* could be very variable because of the specimen for bacterial culture. In Iceland in 2007–2011, NVTs covered 257 isolates (34.9%) in total, including 66 (7.5%) from the middle ear, 152 (27.0%) from the lower respiratory tract, and 39 (22.5%) from invasive specimen.[25]

Although the details had some variations, investigations in localized areas reveal similar data as the national data on the NVT-related pneumococcal disease outbreaks NVTs, especially in countries with balanced economic and health levels. In Hokkaido (the main island of northern Japan), NVTs (especially serotypes 15A, 23A, 11A, 10A, and 35B) increased from 39.7% to 75.1% ($P < .001$) in 2013–2014. Serotypes 15A, 15B, 23A, 24, and 33 F accounted for 27.9% (244/873) of the isolates from children.[26] Since PCV13 was introduced in 2013, NVT-related pneumococcal disease outbreak was also observed nationwide in Japan. The most identified serotypes in the IPD isolates included 19A, 24 F, and 15A. The prevalence of non-PCV13 isolates increased considerably from 51.6% in 2012 to 71.4% in 2014. Among the non-IPD isolates, the most identified serotypes included type 19A, 15A, and 3; the increase in antimicrobial-resistant serotypes 15A and CC63 (Sweden15A-25 clone) was particularly emphasized in a previous study.[27]

The spread of some special serotypes was noticed as a dominant cause of NVT-related pneumococcal disease outbreak. Continuous investigation revealed that the proportion of NVT isolates in children under 5 years of age increased with time in Hong Kong. This proportion of 27.4% in 1999–2000 increased to 29.4% in 2009–2010 and then reached up to 56.4% (88/156) in 2010–2013. The most common non-PCV13 types were 15B (10.3%), 15 C (9.6%), 6 C (7.1%), and 15A (5.1%). Particularly, the carriage of serogroup 15 was more common in vaccinated children.[28] An investigation in Taiwan also found that the most common NVTs were serotypes 15A/F and 15B/C (13.3%), followed by serotype 23A (6.7%). The infections caused by PCV13 serotypes decreased from 83% in 2012–2013 to 44% in 2014–2015, whereas the infections caused by non-PCV13 serotype increased from 17% to 56%.[29] These NVTs may spread to other regions to accelerate the increase of NVTs. Currently, PCV13 is only used in the private sector of mainland China. However, Yan Xu et al.[30] found inpatients with IPDs due to NVTs (types 15A and 15B), which were not identified before the introduction of PCV13. To summarize intuitively the epidemiological characteristics of serotype distribution after PCV13 vaccination, we list Table 2.

2.3 Invasive potential of *S. pneumoniae* expressing NVTs

In addition to the increased popularity of NVTs, researchers have also paid attention to the invasion potential of certain NVTs. The invasive potential of serotypes was estimated as the ratio of IPD-related carriage (odds ratio [OR] and 95% CI) compared with 19A (reference serotype) by meta-analysis. According to reports, serotypes 1, 7 F, and 12 F have higher invasive disease potentials in children aged 0–23 and 0–59 months for all IPDs and clinical syndromes (OR > 5). Several NVTs (6 C, 15A, 15BC, 16 F, and 23B) have lower invasive potential than 19A (OR 0.1–0.3). By contrast, serotypes 8, 12 F, 24 F, and 33 F are at the upper end of the invasiveness spectrum.[32]

Varon et al. found that the number of highly aggressive serotypes in children aged < 2 years old decreased in 2012–2013 compared with the pre-PCV13 period (2008–2009), and only serotypes 24 F and 12 F have high invasiveness.[33] The difference in the invasive potentials between serotypes was reconfirmed by Yildirim et al.[34] In particular, serotype 12 F showed strong invasive potential in several studies. Monali

Table 2. Constituent ratio of NVTs in the era of PCV13 in some studies mentioned above.

		Pre-PCV13 period		Post-PCV13 period		
Country	Age	Year	Non-PCV13-associated IPD	Year	Non-PCV13-associated IPD	Most prevalent serotypes
German[15]	<16 years	-	-	2015–2016	84.1%	-
England[11,17,31]	All	2008–2010	46.1%	2015–2016	80.6%	8, 12 F, 10A, and 9 N
Belgium[21]	Adults	2007–2010	31%	2012–2015	49%	12, 8, and 15 groups
Denmark[23]	All	-	-	2014	71%	-
	0–4 years	-	-	2014	91%	-
	>65 years	-	-	2014	73%	-
India[22]	-	2007		2016	21%	10 F, 9 N, 11A, 20, 15B
Hokkaido[26]	All	2013	39.7%	2014	75.1%	15A, 23A, 11A, 10A, and 35B
Japan[27]	-	2012	51.6%	2014	71.4%	24 F and 15A
Hongkong[28]	-	2009–2010	29.4%	2010–2013	56.4%	15B, 15 C, 6 C, and 15A
Taiwan[29]	-	2012–2013	17%	2014–2015	44%	15A/F, 15B/C, and 23A
Balearic Islands[22]	-	2012–2015	-	2016–2019	58.7%	-
Beijing[30]	-	2014–2016	0%	2017–2019	11.7%	15A and 15B

See text for details on local vaccine use.

et al.[35] compared valid specific data of the population aged 0–4 years from 2011–2017 and >64 years from 2015–2017. They found that serotypes 19A and 3 decreased among infants and children, whereas serotypes 8 and 12 F (contained in NVTs) were common among adults and increased among children in Italy. A national surveillance study in Japan showed that the proportion of 12 F in IPD isolates increased from 4.4% in 2015 to 13.9% in 2016 and further increased to 24.6% in 2017. No increase in 12 F was observed in non-IPD isolates.[36] Similarly, Israel[37] and France[38] reported an increase in IPD and antibiotic-insensitive isolates after the introduction of PCVs, and serotype 12 F was highly pathogenic among the various types of meningitis and pneumonia isolates. Likewise, the IPD outbreak among children in Chiba Prefecture, Japan from 2016 to 2017 may be caused by 12 F. The study clarified the molecular characteristic of 12 F and showed that all of the 26 isolates were ST4846, a unique sequence type to Japan.[39] Hence, strengthening the molecular epidemiological surveillance of these NVTs is necessary.

3. Vaccine effectiveness and NVT-related outbreak in different pneumococcal diseases

The NVTs of *S. pneumoniae* are likely to be the dominant isolates in the post-vaccine period. The serotypes of *S. pneumoniae* are related to specific diseases.[31,40] Therefore, serotype replacement may lead to changes of pneumococcal diseases, and lead to various changes in the incidence of different diseases after PCV administration.

3.1 Pneumococcal meningitis

Surveillance results in England and Wales[11] showed that after the introduction of PCV13, serotypes 12 F, 8, and 10A accounted for about half of pneumococcal meningitis isolates in children under 5 years of age. In all age groups, non-PCV13 types accounted for 80.6% (137/170) of *S. pneumoniae* meningitis isolates in 2015–2016, which is remarkably higher than the 46.1% (143/310) in 2008–2010.[31] By 2015–2016, PCV13-serotype meningitis was rare, and almost all cases were caused by non-PCV13 serotypes. The incidence of VT induced-pneumococcal meningitis among adults in Israel decreased by 70% from 2009 to 2015, but NVT-induced meningitis increased from 0.32/100,000 to 0.75/100,000 (IRR 2.35, 95% CI 1.27–4.35). NVTs (serotypes 15B/C, 6 C, 23A, 23B, and 24 F) that rarely cause IPDs seem to be emerging as the common causes of meningitis.[18] NVTs emerged in 2012–2014; 12 F and 24 F were dominant in the entire population and children, whereas 6 C was common in the elderly; these findings elucidated the impact of PCVs on the evolution of the serotype distribution of pneumococcal meningitis in France.[41] However, a prospective surveillance study did not show a remarkable increase in NVT-induced meningitis for children < 15 years old from 2007 to 2015 in the region of Madrid.[42] In France, the incidence of non-PCV13 meningitis did not increase substantially. Only 24 F was highly pathogenic among the most common serotypes (serotype 15B/C, 22 F, 23B, and 24 F) after the introduction of PCV13.[33]

Although the etiology is associated with many factors, the incidence of meningitis in children is still high. As many as 13/100,000 meningitis cases worldwide were recorded each year in the era of PCVs and *Haemophilus influenzae* type b vaccines.[43] The widespread use of vaccines has led to the emergence of multiple NVT isolates. These isolates usually cannot cause sepsis, but cause meningitis with equivalent illness or more serious manifestation than that of pneumococcal meningitis. The potential reasons could be that NVT isolates do not survive well in the blood; therefore, they may enter the brain route through a non-blood-derived route.[44]

3.2. Pneumococcal pneumonia and empyema

A substantial reduction in the hospitalization burden of pneumococcal pneumonia, all-cause pneumonia, empyema, and lung abscess had been reported since PCV introduction. In Australia, the substantial reduction in the number of pediatric pneumonia hospitalizations and the small increase in the number of empyema hospitalizations were attributed to the introduction of PCV7.[45] *S. pneumoniae* is the most common cause of empyema in children in South Africa, and PCVs has been very effective in reducing the incidence of empyema in children in South Africa.[46] In England, PCV13 has no greater benefit on pneumonia hospitalization than PCV7, but the hospitalization rate of empyema was significantly reduced in children < 2 years of age (RR 0.58, 95% CI 0.34–0.99).[47]

The effect of PCV immunization and the pathogenicity of NVTs showed varied results in pneumonia investigation. The variation could be understood and discussed in view of the complexity of pathogens and the associations of serotype distribution with age and study site. The increase in unspecified pneumonia in high-risk elderlies (>65 years) may partly reflect that this population is more likely to develop pneumonia caused by a low pathogenic serotype, such as certain NVTs, which replace VTs in the nasopharyngeal region. For pneumococcal community-acquired pneumonia, the decline in PCV13 serotypes from 2012 to 2014 was significant for adults aged 50–64 years (P = .032) and adults of all ages (P = .014). In addition, a significant rise in incidence rates was noted from 2014 to 2015 in adults aged 50–64y, ≥65y and ≥50 y (P = .019, 0.022, 0.018, respectively).[48] Only PCV13 serotype distribution was associated with age. Pneumococcal community-acquired pneumonia was attributable to PCV13 serotype in 25.6%, 33.0%, and 41.4% of adults aged 16–49, 50–64, and ≥65 years, respectively.[49] PCV13 was effective in preventing VT-IPDs but not community-acquired pneumonia from any cause among older adults. The 46% reduction in VT community-acquired pneumonia after PCV13 immunization indicated that this immunization may contribute to a reduction in pneumococcal pneumonia in older adults.[50] Some investigations suggested that the pathological characteristics of pneumonia could change because of NVT-related pneumococcal disease outbreak. In Utah, a retrospective review of all children aged < 18 years with pneumococcal necrotizing pneumonia showed that non-

PCV7 serotypes comprised 49% of the isolates in 1997–2000 and 88% of isolates in 2001–2006 (OR 7.89, 95% CI 2.91–21.90).[51]

3.3. Pneumococcal otitis Media (OM)

The serotype distribution of isolates that cause pneumococcal OM also demonstrated serotype replacement following PCV immunization. Serotype 19A and serogroups 11 and 15 were the major nasopharyngeal-colonizing bacteria in Korean children with OM after the introduction of PCV7.[52] The prevention rate of VT-induced acute OM was only 56%–67%. Medical records of pneumococcal OM cases in a tertiary pediatric hospital showed that the composition of NVTs increased greatly after the introduction of PCV13. The distribution of pneumococcal serotypes before (1999–2005), after PCV7 (2006–2010), and after PCV13 (2011–2014) changed year by year as follows year: 81%, 25%, and 0% for PCV7 serotypes ($P < .0001$); 16.3%, 70.8%, and 63.6% for PCV13 serotypes ($P < .0001$); and 2.3%, 4.1%, and 36.3% for non-PCV13 serotypes ($P = .0002$), respectively.[53] In Iceland, the proportion of NVTs (serotypes 6 C, 15B/C, 23A, and 23B) in *S. pneumoniae* isolates from the middle ear of children with acute OM increased considerably between 2009 and 2017. The NVTs in pneumococci that increased post-PCV in <2 years were serotypes 15B/C ($n = 1–40$; $P < .001$), 6 C ($n = 1–29$; $P < .001$), 23A ($n = 2–18$; $P > .007$), and 23B ($n = 1–10$; $P = .042$). Serotype 15B/C was the only NVT that increased in 2–4 years ($n = 1–11$; $P = .042$), and serotype 6 C ($n = 12$) was only detected post-PCV within the same age group.[54] Between 2008 and 2016, the rate and diversity of non-PCV13 serotypes increased in two Spanish provinces (Gipuzkoa and Barcelona), and an emerging clone causing OM was detected in each region: serotype 23B-ST2372 in Gipuzkoa and serotype 11A-ST838/ST6521 in Barcelona.[55]

4. Potential factors affecting the NVT-related outbreak of *S. pneumoniae*

The association between increased NVTs and PCVs immunization is well demonstrated. However, inconsistent findings were also observed. On the one hand, the NVT-related pneumococcal disease outbreak was not found in some countries and regions where PCVs was included in the immunization program. For example, no remarkable change in the IPD incidence caused by non-PCV13 was observed in Madrid, Spain from 2007 to 2016. In short, the influence of PCV13 on IPDs has not been replaced by other serotypes not covered by the vaccine.[56] On the other hand, prevalent NVTs were also observed in some countries or regions where PCVs was not widely used or even not used. For instance, non-PCV13 isolates, including the common serotypes 34 and 23A, accounted for 45.2% of the *S. pneumoniae* isolates from hospitalized children in Zhongjiang County of Sichuan Province in 2015, serotype 34 taking the third place in the common serotypes.[57]

Non-vaccine factors may influence the recorded rates of serotype-specific disease and therefore confound the interpretation of the relation between PCV introduction and changes in serotype distribution.[58] Factors, including variation in the proportion of isolates serotyped before and after vaccine introduction, changes in blood culture practice, secular trends, and pneumococcal disease outbreaks, should be considered in interpreting surveillance data on pneumococcal disease[1].

4.1 Possible insufficiency of herd protection in the aging population

Vaccination in children produces "herd protective effect,"[59] which almost eliminated VT-IPDs in adults.[60,61] PCV7-induced population protection continued, and similar indirect protection occurred in other serotypes covered by PCV13.[11]

However, the herd protection effect seems to have reached its limit. Serotype replacement occurred in adult cases of pneumococcal pneumonia following the vaccination of children with PCV7 in Japan.[62] In Ireland, a 94% reduction in PCV7 serotypes from 2007–2008 to 2015–2016 (IRR 0.05, $P < .0001$) was observed, whereas the incidence of NVT-IPDs increased significantly (IRR 3.43, $P = .0001$). Consequently, the overall incidence rate of IPDs in adults has remained relatively unchanged (from 28.66/100,000 to 28.88/100,000, IRR 1.01, $P = .9477$).[63] Infant PCV immunization provided indirect protection against IPDs in adults in Germany after more than 10 years since its implementation. The reported cases of IPDs in children under 2 years of age dropped from 11.09/100,000 in 2003–2006 to 5.94/100,000 in 2017–2018, whereas a remarkable overall increase in IPD cases was found in adults, particularly over 60 years old from 1.64/100,000 to 10.08/100,000.[64]

A meta-analysis showed that PCV13 for children has moderate impact on reducing overall IPD and VT-IPDs, but adult NVT-IPDs has increased considerably, particularly in adults over 65 years of age.[65] In brief, the potential benefits of PCV13 immunization for the elderly had been gradually diminishing. Five years after PCV10/PCV13 introduction in Europe, the incidence of IPDs caused by non-PCV13 serotypes increased by 63% (95% CI 39%–91%). IPDs caused by the PCV13 serotypes in the elderly are gradually decreasing, whereas IPDs caused by non-PCV13 serotypes are gradually increasing.[66] In Sweden, IPD incidence decreased between 2005 and 2016 in vaccinated children (by 68.5%) and in the whole population (by 13.5%) but not among the elderly (increased by 2%) because of the substantial increase in NVTs. In 2016, NVTs constituted 72% of IPDs in the elderly.[67] Among adults aged 50–64 years old, a 26% increase (95% Index Error [IE]13–44) in non-PCV13 IPDs was detected in 2012–2013 in the USA.[9] Moreover, remarkable differences in the incidence of different serotypes were observed in adults over 40 years old. Serotypes 3, 8, and 12 F have a higher potential to cause IPDs in the elderly than expected based solely on the carriage and invasiveness of PCVs in children.[68]

If NVTs were prevalent and displayed more invasive ability in the adult population than in children, then it will likely increase IPDs in the crowd. The IPD incidence of seven common NVTs in Denmark was low in the age groups of 0–4 and 5–64 years but relatively high in the >65 years old age group. Invasive capacity differs among serotypes and age. NVTs may spread more frequently in adults than in children, that is, adults are more prone to be infected by NVTs than

children.[22] Serotypes 1, 7 F, and 12 F were the most aggressive in all age groups. Serotypes 1, 9 V, and 18 C were considerably more aggressive in children than in adults, whereas serotypes 3, 6A/C, 8, and 11A were markedly more aggressive in adults than in children.[68] Besides, pediatric isolates expressing types 22 F and 33 F formed biofilms that are superior to adult isolates and may be beneficial for nasopharyngeal colonization in children. Therefore, these isolates are important for the carriage and subsequent transmission of PCVs to the elderly. Thus, the emergence of type 22 F may be due to the enhanced ability of this serotype to evade host immune response.[65]

Finally, we cannot rule out that in some areas, the proportion of NVTs in adults was high before the introduction of the vaccine. In Zhongjiang County where PCV13 vaccination rate was very low in 2018–2020, the proportion of non-PCV13 type increased remarkably with the increase of age (28.7% at 2 years old to 58.1% at≥60 years old). The study suggests that adults, especially the elderly, may be non-PCV13 -type repositories.[69] The distribution characteristics of serotypes in adult may be different from those in children; hence, continuous monitoring in a larger geographic area and age group is required to verify this hypothesis. The role of PCV13 in the elderly is still being explored.[70] The key to solving this problem may be the clarification of the current distribution of *S. pneumoniae* serotypes in the elderly. The current trend among the aging population is becoming increasingly serious; thus, the burden of IPDs in the elderly cannot be ignored. Therefore, clarifying the impact of NVTs on adults, especially those with underlying diseases or risk factors (including immunosenescent adults aged > 65 years) is particularly important to provide reliable guidance. Expanding infant-administered PCV valency is likely to result in diminishing returns, and the complementary pairs of infant- and adult-administered vaccines could be a superior strategy.[71]

4.2 Emergence of drug-resistant NVT isolates

Undoubtedly, antibiotics and vaccines are powerful tools that control *S. pneumoniae* infection. They have strong selective pressure for these bacteria when they are frequently used in the population. The problem that cannot be ignored was that the resistance of *S. pneumoniae* to commonly used antibiotics increased markedly and spread rapidly because of the extensive use of antibiotics.[72,73] The serotype of drug-resistant isolates could not be covered by the present PCVs. Serotype 19A was an example. Researchers formerly exhibited that the spread of multidrug-resistant capsular-type 19A isolates was due to antibiotic abuse in developing countries.[74] After the introduction of PCV10, the frequency of 19A increased, which was accompanied by a selection of CC320 and antimicrobial resistance.[75] The detection rate of 19A serotype, which is the most penicillin-resistant serotype, has increased rapidly in Shenzhen in the past 10 years. Now, 19A is highly resistant to penicillin under the pressure of antibiotics and may spread further. Similarly, the average minimum inhibitory concentration of penicillin for NVTs is 0.8888 mg/mL, which is still much higher than those reported in some countries where antibiotics are strictly used. Otherwise, penicillin-resistant NVT *S. pneumoniae* will spread widely and reduce the efficacy of PCV13.[76] Therefore, controlling the overuse of antibiotics and avoiding the emergence of NVT *S. pneumoniae* that is highly resistant to penicillin are urgently needed. In 2010, penicillin-resistant PCV13 serotypes (including 15A, 35B, and 23B) in children increased in Ireland, which suggested that NVT-related pneumococcal disease outbreak was probably related to the acquisition of resistant strains.[77]

Antibiotics may affect the transmission of NVTs in two ways: NVT-resistant strains are selected along with vaccine promotion, or the prevalence of NVT-resistant strains had begun before PCV administration because of antibiotics abuse. Previous studies suggested that PCV13 provides a powerful strategy to combat the antimicrobial resistance of *S. pneumoniae*.[78] This might be caused by the formulation of early PCVs were based on the serotype distribution under antibiotic selective pressure. Currently, both selective pressures exist with remarkable regional differences, which will make the conditions variable for *S. pneumoniae* infection outbreak. The potential relationship between antibiotic selective pressure and serotype replacement reminds us that antibiotics should be used properly to ensure that PCVs remains a powerful tool in the fight against antibiotic resistance in *S. pneumoniae*.

4.3 Capsule conversion and vaccine escape hypothesis

VT and NVT strains can coexist in the nasopharynx. Capsule genes can be horizontally recombined, which results in a capsule switch from VTs to NVTs or from less virulent NVTs to more virulent NVTs. The elimination of VTs through the use of PCVs promoted the spread of preexisting minor clones, as well as of novel clones arising from genetic exchange.[79]

The increase in serotype 19A can be explained in part by the expansion of a genotype that has been circulating in the USA before vaccine implementation (and other countries since at least 1990), as well as the emergence of a novel "vaccine escape recombinant"[80] pneumococcal isolate. This isolate has a genotype that was previously only associated with serotype 4 but now expresses a non-PCV7 19A capsule. Brueggemann et al.[80] characterized the putative recombination event that leads to the envelope site from VTs to NVTs. Sequencing the capsular locus flanking regions of 51 vaccine escape (progeny), recipient, and putative donor pneumococci revealed a 39 kb recombination fragment, including capsular locus, flanking regions, and two adjacent penicillin-binding proteins, and thus resulted in a capsular switch and penicillin non-susceptibility in a single genetic event. Since 2003, thirty-seven such vaccine escape strains have been detected, and some of which had evolved further. Furthermore, two new types of 19A vaccine escape strains emerged in 2005. This finding is the first single recombinational event documented in vivo that resulted in a change of serotype and penicillin nonsusceptibility. Vaccine escape by genetic recombination at the capsular locus has the potential to reduce PCV7 effectiveness in the long term.[80] In Italy,[81] two serotype 19A (ST695) *S. pneumoniae* vaccines escaped the recombinant strains caused by a capsule switching event, which is rare in Europe.

PMEN3 (Spain9V-156), a penicillin-non-susceptible clone of *S. pneumoniae*, caused IPDs in Barcelona in 1987–2016. Evidence of recombination events was showed mostly in three regions, namely, the capsular operon (associated with capsular switching) and adjacent regions containing *pbp2x* and *pbp1a*, the *murM* gene, and the *pbp2b–ddl* region. Some of these genetic changes resulted in successful new variant serotype lineages, including one variant of serotype 11A that is not currently included in the PCV13.[82] In the UK, the serotype of a *S. pneumoniae* meningitis isolate was originally serotype 14 in PCV13 and was converted into serotype 28A in NVTs through the capsule; this serotype replacement caused diseases by avoiding the immune defense and preventive effects of vaccines.[83]

Serotype 35B, which is resistant to penicillin, increased the incidence of IPDs in 2001–2009. The further increase after the implementation of PCV13 in 2010 was caused by 35B/ST558 clones. The 9 V/ST156 clones of 35B/ST558 and VTs were the donor and recipient of 35B, respectively. The capsular transition events in six states in the US in 2015–2016 led to the occurrence of 35B/ST156 clones.[84] The spread of 35B/ST156 caused a major concern, because ST156 strains, which have pathogenicity and belong to VTs, were previously dominant in the world.

The widespread use of PCVs can promote the emergence of new serotypes, such as the large number of *cps* loci of *Streptococcus oralis*, through interspecific recombination.[85] The emergence of serotype 10D is precisely due to this reason. Genetic analysis showed that type 10D *cps* has three large regions syntenic to and highly homologous with the *cps* loci from serotype 6 C, serotype 39, and an oral *Streptococcus* strain (*S. mitis* SK145). The 10D *cps* region syntenic to SK145 is about 6 kb and has a short gene fragment of *wciN* at the 5′ end. The presence of this nonfunctional *wciN* fragment provided compelling evidence for a recent interspecies genetic transfer from oral *Streptococcus* to *S. pneumoniae*.[86] A whole-genome sequence analysis of sixty-seven serotype 1 isolates collected prior to PCV13 introduction showed recombination hotspots in four virulence genes and more notably in the cps locus (*cps2L*), which potentially lead to capsular switching, a major mechanism of the emergence of NVTs.[87]

S. pneumoniae infection is one of the many engraftments and upper respiratory tract infections caused by *Streptococcus*. Sometimes, the capsular polysaccharides of *S. pneumoniae* are not easy to distinguish from those of other bacteria in serology. Different structures of the interaction between bacteria and the related specific immune response caused by capsular polysaccharide still need further research. Although capsular conversion and vaccine-escaping strains are unlikely to have a remarkable impact on the immune response to PCV, serotype distribution and molecular epidemiological surveillance at all ages are necessary to monitor the long-term effects of PCVs.[83]

4.4 Complexity of vaccine selection and schedule

Substantial evidence shows the impact of each schedule on the disease in various routine use settings. PCV10 and PCV13 have been proven safe and effective and have direct (in vaccinated individuals) and indirect (in unvaccinated individuals living in communities with vaccinated children) effects against pneumococcal disease caused by vaccine serotypes when used in a three-dose (2p+1 or 3p+0) or four-dose schedule (3p+1).[1,59]

Different vaccination doses may affect the carriage of nasopharyngeal NVTs in children. Compared with the control group, the influence of PCVs on the VTs of *S. pneumoniae* had no substantial difference between 4 and 6 months and between one and two doses. However, nine VT carriers (RR = 0.67, n = 7613 infants) and eight NVT carriers (RR = 1.23, n = 5861 infants) were recorded in 7 months, which indicates that the serotypes in the NVTs of *S. pneumoniae* carriers vary substantially between one and three doses.[88] The choice of vaccination program may cause subtle differences in serotype replacement between vaccinators and their contacts. Three doses of basic immunization were associated with an increased risk of NVT pneumococcal carrier, and three doses of PCV considerably reduced the pneumococcal carrier of VTs compared with no PCV vaccination. Three doses had more substantial effects than one or two doses. Although the difference did not reach statistical significance, it may reflect a clinically important dose response. Children immunized with 2p+1 PCV13 had a 72% increase whereas children immunized with 3p+1 had a 38% increase in the rate of colonized NVT *S. pneumoniae* compared with children immunized with other vaccines or placebo and unimmunized children.

The Joint Committee on Vaccination and Immunization in the UK proposed to replace the 2 + 1 procedure with the 1 + 1 procedure. Wasserman et al.[89] found that the incidence of IPDs is expected to increase in all age groups by model analysis. In the 5 years from 2018, the model study showed that 23,638 cases of IPDs in all age groups might occur if the 2 + 1 procedure is implemented. However, a multicenter parallel-group randomized controlled trial[90] showed that for 9 of the 13 serotypes in PCV13, the infants treated with a single dose had an enhanced response that is equal to or superior to the response observed according to the standard 2 + 1 procedure in the UK. In countries with mature pneumococcal vaccine programs and established herd immunity, maintaining the population control of VT-induced pneumococcal disease is possible by adopting a 1 + 1 schedule. A number of randomized controlled studies comparing a 1 + 1 PCV schedule with existing immunization schedules in India, South Africa, Vietnam, and Gambia are currently underway. These studies, together with IPD surveillance and carriage studies, will provide the comprehensive evidence for future decisions about global PCV immunization strategies.

In addition, Converso et al.[84] pointed out that serotype replacement can be thought of as a result of PCV application, that is, adding a new serotype into the vaccine will increase the complexity and cost of production and can make an already costly vaccine more inaccessible in developing countries.[91] The pneumococcal prevalence rate is higher in developing countries, and health system resources are limited; thus, the development of a new vaccine unrelated to capsular polysaccharide (such as whole cell vaccine, protein vaccine, mucosal vaccines, and multivalent protein hybrid pneumococcal vaccines)[92–96] may cope with the huge pneumococcal disease burden worldwide. Pneumococcal surface protein A has been successfully tested as a vaccine candidate against *S. pneumoniae* infections.[97]

5. Challenges and future prospects

The increased prevalence and pathogenicity of NVTs pose new challenges to the reduction of the burden of pneumococcal disease, which was a benefit from widespread PCV vaccination. The pathogenicity of this organism, the manifestation of clinical diseases caused by *S. pneumoniae*, and the preventive effect of PCV immunization with the spread of NVTs are varied. Multiple factors, including antibiotic abuse, PCV immunization, NVTs' original reservoir, and the spread of NVTs, are shaping the epidemiology of *S. pneumoniae*. There is no doubt that the limited dissemination of VTs caused by universal PCVs vaccination played important role in spread of NVTs. The epidemic of NVTs is just one piece of evidences to prove the effectiveness of PCVs.

It is not a long-term solution to add more serotypes in the PCVs. The high cost of high-valent PCVs commodities limits their popularity in developing countries with high disease burdens. Furthermore, the distribution of disease-causing serotypes varies geographically and includes more types covered in a single current PCV formulation.[98] Therefore, persistently monitoring the epidemiological characteristics of *S. pneumoniae* in the coming years is necessary for regions or countries with or without PCV immunization. The effects of serotype replacement on public health vary geographically.[99] Producers should tailor their vaccines to different regions on the basis of real epidemiological data. Overall, emerging and spreading NVTs can be regarded as the focus for future serotype epidemiological survey and vaccine optimization.

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