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RESEARCH PAPER

Serotype distribution of *Streptococcus pneumoniae* and potential impact of pneumococcal conjugate vaccines in China: A systematic review and meta-analysis

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ABSTRACT

Objective: Thirteen-valent pneumococcal conjugate vaccines (PCV13) was licensed for optional use in mainland China since 2017, but the uptake is low. To update the research evidence for the pneumococcal serotype distribution of pre-PCV era and to estimate the potential impact of PCVs, we performed a meta-analysis on the relevant publications concerning the Chinese population.

Methods: This systematic review and meta-analysis were conducted on the pneumococcal serotype distribution publications in mainland China from 2000 to 2016. The literature was searched in PubMed, Ovid-EMBASE, Web of Science, CNKI and Wanfang. Heterogeneity and publication bias were tested by I^2, meta-regression, Egger's and Begg's test. The pneumococcal serotype and vaccine serotype coverage rates were pooled using the random-effects model in Stata SE 12.0.

Results: In total, 85 publications were included. **Of all 16,945 included** pneumococcal **isolates, the most common serotypes/serogroups were 19F, 19A, 23F, 14, and 6B, that** from children were the same as above, that from adults≥18 years were 19, 3, 6, 23, and 14. Among isolates from children <18 years, the pooled coverage for PCV10 serotypes was 52.3%, that for PCV13 was 68.4% and that for PPSV23 was 65.5%. Regarding individuals ≥18 years, the pooled coverage for PCV10 serotypes was 29.7%, that for PCV13 was 49.5% and that for PPSV23 was 50.7%. Serotype prevalence and vaccine serotype coverage varied by age group, source, and region.

Conclusions: The most common pneumococcal serotype in mainland China was 19F. The serotype coverage rates of PCV13 and PPSV23 were 50%–68% in mainland China.

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Introduction

Streptococcus pneumoniae is an important cause of community acquired infections and is associated with significant morbidity and mortality worldwide. By the end of the 20th century, pneumonia was the first and second leading cause of death among children aged under 5 years in the rural and urban areas of China, respectively.[1] *S. pneumoniae* causes at least 18% of severe episodes and 33% of deaths from pneumonia worldwide.[2] The burden of invasive pneumococcal diseases (IPD) has decreased substantially due to the widespread usage of pneumococcal conjugate vaccines (PCVs) worldwide.[3,4] However, *S. pneumoniae* still poses a significant burden on individuals and healthcare systems because of the high costs of PCVs and the serotype shift after immunization.[5]

S. pneumoniae has more than 90 serotypes, which vary by age and different regions. Only when the distribution of *S. pneumoniae* and the serotype coverage of PCVs or pneumococcal polysaccharide vaccine (PPSV) are well-known can useful information be offered to guide the vaccination program. In mainland China, 7-valent pneumococcal conjugate vaccine (PCV7) was licensed as type II self-paid vaccine for optional use in 2008 but the extent of adoption was very low. PCV13 has been licensed for optional use since November 2016. However, it won't be widely used due to low awareness and high price. In 2013, WHO provided a new plan that the completed vaccination coverage rate of PCVs should reach 90% to avoid severe pneumonia in children by 2025.[6] Before the use of PCV13 around China, it is important to update the research evidence for pneumococcal disease. Currently, many papers have reported on pneumococcal serotypes in mainland China, but there is a lack of evidence of the pneumococcal serotype distribution countrywide and in all age groups. A recently published manuscript has reviewed the pneumococcal serotype distribution and coverage among Chinese children, but they did not include isolates from adults or provide detailed information regarding the serotype distribution and vaccine serotype coverage by age group.[7] Thus, to provide a comprehensive view of the pneumococcal isolate characteristics and estimate the potential impact of vaccines in China, we performed a systematic review and meta-analysis of publications on serotype distributions of pneumococcal infections in mainland China from 2000 to 2016.

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Results

Literature characteristics

In total, 1,848 potentially related articles were identified, and 384 articles were duplicated. Of these articles, 123 were identified as potentially relevant articles according to the screening of the titles and abstracts. Six articles were excluded because they were reviews, 16 articles shared the same data, and 4 articles had a sample size that was too small. Finally, 85 articles were included in our meta-analysis (Fig. 1). The characteristics of the included articles were listed in Table 1. The regional distribution of the enrolled articles and pneumococcal isolates are shown in Fig. 2.

Of the included articles, 72 articles used the capsular Quellung test for serotyping, 7 used multiplex PCR, 6 used both capsular Quellung test and multiplex PCR; 58 articles only included isolates from children, and 3 articles only reported isolates from adults; 12 articles studied the invasive isolates, and 32 reported both invasive and non-invasive isolates.

Pneumococcal serotypes

Pneumococcal isolates

In total, 16,945 *S. pneumoniae* isolates were eventually included in this meta-analysis; 11,987 (70.7%) isolates were from children younger than 18 years, 1,963 (11.6%) isolates were from adults, and the other 2,995 isolates were from children or adults. There were 896 (5.3%) invasive isolates, 7,577 (44.7%) non-invasive isolates (the stratification analysis on invasive / non-invasive isolates were only done for children), and the other 8,503 isolates could not be stratified. Stratifying by geographical regions, 9,442 (55.7%) strains were from the south, 3,608 (21.3%) strains were from the north, and the other 3,895 isolates were from multicenter that could not be stratified.

Serotype distribution and vaccine serotype coverage

Of all the included isolates, the most common serotypes were 19F, 19A, 23F, 14, 6B, 6A, 3, 15B, 9V, and 5. The main difference of serotype distribution between children and adults was that serotype 3 was more prevalent in adults than in children. **For those isolated from sterile sites in children, the most common s**erotypes/serogroups **were** 19F, 19A, 14, 23F, and 6B. Although serotype 19A and serotype 14 were more prevalent in invasive strains than in non-invasive strains, serotype 6A in invasive strains was far less than in non-invasive strains.

Fifty-five point seven percent of the included isolates were from the south of mainland China, and 21.3% were from the north. Serotype 19A and serotype 6B were more prevalent in

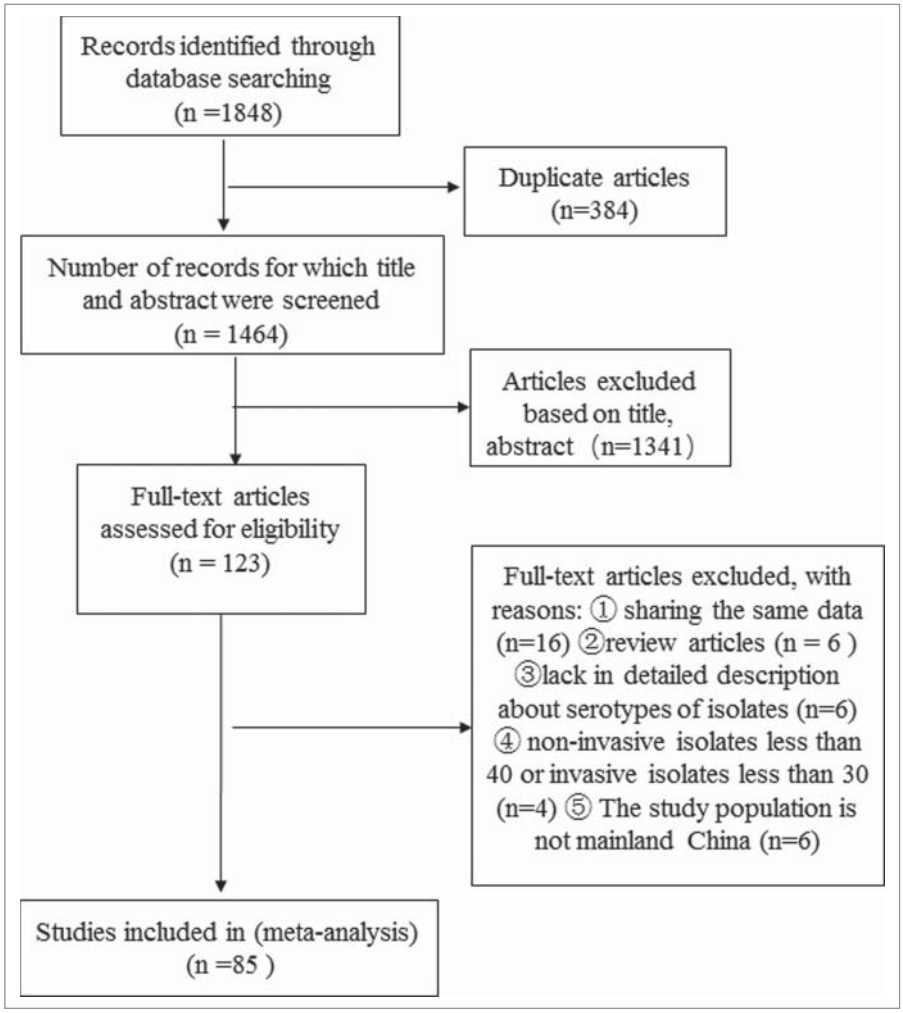

Figure 1. Selection of Articles for Meta-analysis.

Table 1. Characteristics of the included studies published from 2000 to 2016 in mainland China.

	First Author	Study Year	Age (y or m)	Location in China	Source	Number of strains	Serotype method	Vaccine Coverage Rate [a]		
								PCV10	PCV13	PCV23
South										
	Yang F[20]	1996–1999	All age	Shanghai	Non-invasive	111	Quellung	50.5%	71.2%	70.3%
	Yang F[21]	1997–1998	≤5 y	Shanghai	Non-invasive	222	Quellung	56.8%	73.9%	60.8%
	Li ZF[22]	1999–2001	2–14 y	Guangzhou	Non-invasive	84	Quellung	32.1%	46.4%	39.3%
	Zhao GM[23]	2000-2001	≤3 y	Shanghai	Non-invasive+invasive	112	Quellung	72.3%	81.3%	72.3%
	Wang CQ[24]	2000–2001	<18 y	Shanghai	Non-invasive	96	Quellung	61.5%	71.9%	62.5%
	Wang CQ[25]	2000-2002	1m-15 y	Shanghai	Non-invasive	111	Quellung	64.9%	74.8%	64.9%
	Luo XM[26]	2003	All age	Zhongshan	Non-invasive	266	Quellung	37.6%	53.0%	48.1%
	Sun ZY[27]	2003-2004	<5	Wuhan	Non-invasive	133	Quellung	5.3%	6.0%	6.0%
	Zhang J[28]	2004	unknown	Wuhan	Non-invasive	152	Quellung	4.6%	6.6%	7.2%
	Zhang J[29]	2004	<18 y	Wuhan	Non-invasive	114	Quellung	6.1%	7.0%	7.0%
	Liu YK[30]	2004-2005	All age	Wuhan	Non-invasive	304	Quellung	4.6%	6.6%	7.2%
	Yang F[31]	2004–2005	>18 y;<12 y	Shanghai	Non-invasive	103	Quellung, PCR	71.8%	84.5%	86.4%
	Ren HY[32]	2004–2006	<18 y	Chengdu	unknown	123	Quellung	52.0%	60.2%	68.3%
	Zhang XH[33]	2004–2009	≥18 y	Hunan	Non-invasive+invasive	822	Quellung	5.1%	20.6%	20.6%
	Pan W[34]	2005–2012	<18 y	Nanjing	invasive strain	155	Quellung	61.3%	80.6%	85.8%
	Yang T[35]	2005–2013	All age	Guangdong	Non-invasive+invasive	383	Quellung	16.4%	21.9%	21.9%
	Zhao RZ[36]	2006–2007	≤5 y	Shenzhen	Non-invasive+invasive	90	Quellung	95.6%	98.9%	100.0%
	Deng QL[37]	2006-2007	1m—6 y	Guangzhou	Non-invasive	79	Quellung	94.9%	94.9%	97.5%
	Dong YS[38]	2006–2008	All age	Chongqing	Non-invasive+invasive	143	Quellung	8.4%	10.5%	15.4%
	Dong YS[39]	2006–2008	unknown	Chongqing	Non-invasive+invasive	133	Quellung	4.5%	4.5%	4.5%
	Zhang H[40]	2007–2008	≤5 y	Shanghai	Non-invasive	338	Quellung	57.7%	81.1%	80.5%
	Xu F[41]	2007–2010	<18 y	Nanjing	invasive	48	Quellung	70.8%	93.8%	95.8%
	Miao DQ[42]	2007–2011	<18 y	Nanjing	Non-invasive+invasive	323	PCR	44.0%	73.7%	62.8%
	Hu JY[43]	2009	12–18 m	Shanghai	Non-invasive	102	Quellung	63.7%	77.5%	71.6%
	Zhao DF[44]	2009	12–18 m	Wuhan	Non-invasive	75	Quellung	38.7%	54.7%	46.7%
	Zhang C[45]	2009–2010	All age	Sichuan	Non-invasive+invasive	166	Quellung	10.2%	12.0%	16.9%
	Li JP[46]	2009–2010	<18 y	Zhejiang	Non-invasive	106	Quellung	59.4%	95.3%	92.5%
	Ying QH[47]	2009–2010	All age	Shaoxing	Non-invasive+invasive	103	Quellung	62.1%	62.1%	62.1%
	Zhang B[48]	2009-2010	All age	Chongqing	Non-invasive+invasive	91	Quellung, PCR	61.5%	75.8%	81.3%
	Chen DL[49]	2009-2011	All age	Maanshan	Non-invasive+invasive	80	Quellung	55.0%	83.8%	82.5%
	Ma X[50]	2009-2012	<14 y	Shenzhen	invasive	87	Quellung	72.4%	81.6%	81.6%
	Lin XF[51]	2009-2013	≥18 y	Wenzhou	invasive	52	Quellung	59.6%	90.4%	86.5%
	Zhou K[52]	2009-2013	<12 y	Nanjing	invasive	51	Quellung	76.5%	96.1%	98.0%
	Jing CM[53]	2009-2014	<18 y	Chongqing	Non-invasive+invasive	600	Quellung	53.0%	62.8%	62.8%
	Kang LH[54]	2010-2013	≤11 y	Chongqing	Non-invasive+invasive	83	Quellung, PCR	51.8%	79.5%	73.5%
	Lu C[55]	2010-2013	≤14 y	Shenzhen	invasive	76	Quellung	72.4%	94.7%	97.4%
	Liu MJ[56]	2010-2013	≤11 y	Chongqing	Non-invasive+invasive	46	PCR	52.2%	84.8%	78.3%
	Song XQ[57]	2010-2014	0-6 y	Taizhou	Non-invasive	322	Quellung	82.9%	95.7%	95.7%
	Li M[58]	2011-2012	≤5 y	Humen	Non-invasive	229	Quellung	95.2%	97.4%	97.8%
	Huang SY[59]	2011-2013	All age	Guangzhou	Non-invasive+invasive	94	Quellung	50.0%	67.0%	67.0%
	Ding YF[60]	2011-2013	< 18 y	Suzhou	Non-invasive	79	PCR	55.7%	93.7%	93.7%
	Jiang QH[61]	2011-2013	>18 y	Shanghai	Non-invasive+invasive	37	Quellung, PCR	37.8%	48.6%	51.4%
	Wang JR[62]	2011-2014	0-107m	Wenling	unknown	284	Quellung	60.6%	85.9%	80.6%
	Wang LM[63]	2011-2015	0-6 y	Jinhua	Non-invasive	302	Quellung	83.8%	97.7%	97.7%
	Li ST[64]	2012	1-10 y	Nanjing	Non-invasive	584	Quellung	64.7%	92.3%	96.4%
	Fen P[65]	2012	0-14 y	Shanghai	Non-invasive	328	Quellung, PCR	58.2%	84.1%	77.4%
	Yuan YT[66]	2012-2013	<7 y;>50 y	Xiamen	Non-invasive+invasive	265	Quellung	62.6%	77.4%	67.5%
	Geng Q[67]	2012-2013	≤5 y	Suzhou	Non-invasive	175	PCR	66.3%	84.6%	84.6%
	Fen P[68]	2013	≤14 y	Shanghai	Non-invasive+invasive	284	Quellung, PCR	58.1%	81.0%	79.9%
	Peng YJ[69]	2015	≤12 y	Chongqing	Non-invasive	267	Quellung	49.1%	72.7%	66.7%
North										
	Yu SJ[70]	1997	≤5 y	Beijing	Non-invasive	190	Quellung	31.6%	44.7%	31.6%
	MCGEE L [71]	1997-1998	≤5 y	Beijing	Non-invasive	376	Quellung	47.1%	74.7%	55.1%
	Li J[72]	1999	≤5 y	Beijing	Non-invasive	97	Quellung	8.2%	10.3%	11.3%
	Yao KH[73]	2000-2002	<5 y	Beijing	Non-invasive	63	Quellung	4.8%	4.8%	6.3%
	Yao KH[74]	2000-2004	≤5 y	Beijing	Non-invasive	129	Quellung	7.0%	7.0%	7.8%
	Yu S[75]	2000-2005	≤5 y	Beijing	Non-invasive	519	Quellung	8.3%	8.5%	11.6%
	Tong YJ[76]	2004	≤5 y	Beijing	Non-invasive	137	Quellung	10.2%	10.2%	14.6%
	Wu JX[77]	2008-2010	≤6 y	Linyi	Non-invasive	124	Quellung	29.8%	48.4%	71.8%
	Liu CF[78]	2009-2011	3m-5 y	Shenyang	invasive	61	Quellung	52.5%	93.4%	100.0%
	Zhou L[79]	2010	≤5 y	Beijing	Non-invasive	140	Quellung	37.1%	44.3%	37.1%
	Wang TW[80]	2010-2013	≤5 y	Dalian	Non-invasive	131	PCR	60.3%	60.3%	60.3%
	Cao XH[81]	2012	<18 y	Luohe	Non-invasive+invasive	134	Quellung	48.5%	48.5%	59.0%
	Li J[82]	2012-2014	<18 y	Beijing	Non-invasive+invasive	103	Quellung	59.2%	86.4%	80.6%
	Liu ZW[83]	2013-2014	≤3 y	Taian	Non-invasive+invasive	320	Quellung	75.0%	82.8%	75.0%
	Dong F[84]	2013-2014	<18 y	Beijing	Non-invasive+invasive	258	Quellung	43.0%	65.5%	64.0%
	Yao KH[85]	2013-2014	≤14 y	Beijing	Non-invasive+invasive	187	Quellung	25.7%	55.1%	46.0%
	Yu SJ[86]	2013-2014	≤16	Beijing	Non-invasive	100	Quellung	39.0%	51.0%	44.0%
	Zhou MJ[87]	2013-2015	All age	Baoding	Non-invasive+invasive	210	PCR	35.2%	62.9%	51.9%

(*Continued on next page*)

Table 1. (*Continued*)

	First Author	Study Year	Age (y or m)	Location in China	Source	Number of strains	Serotype method	Vaccine Coverage Rate [a] PCV10	PCV13	PCV23
Multicenter	Wang Q[88]	2013-2016	3m—7.5 y	Beijing	invasive	30	Quellung	56.7%	96.7%	93.3%
	Wang JF[89]	2014	<18 y	Zhengzhou	Non-invasive+invasive	134	Quellung	48.5%	48.5%	59.0%
	Wang YT[90]	2014	≤8 y	Hebei	invasive	43	PCR	48.8%	65.1%	67.4%
	Zhang M[91]	2014-2015	<18 y	Jinan	Non-invasive	42	Quellung	9.5%	9.5%	23.8%
	Yao KH[92]	2000-2002	<5 y	Multicenter	Non-invasive	625	Quellung	6.6%	6.6%	6.6%
	Li MC[93]	2004-2009	unknown	Multicenter	unknown	144	Quellung	8.3%	9.0%	10.4%
	Li MC[94]	2004-2011	unknown	Multicenter	Non-invasive+invasive	241	Quellung	58.9%	76.8%	74.3%
	Liu YD[95]	2005-2006	≤4 y	Multicenter	Non-invasive+invasive	451	Quellung	63.6%	75.4%	75.4%
	Xiao SK[96]	2005-2008	All age	Multicenter	Non-invasive+invasive	580	Quellung	31.7%	52.6%	52.6%
	Liu CL[97]	2005-2008	All age	Multicenter	invasive	148	Quellung	36.5%	67.6%	66.2%
	Zhao CJ[98]	2005-2011	All age	Multicenter	Non-invasive+invasive	240	Quellung	34.6%	63.8%	63.8%
	Yao KH[99]	2006-2007	≤5 y	Multicenter	Non-invasive+invasive	279	Quellung	81.4%	92.8%	93.9%
	Yao KH[100]	2006-2008	≤5 y	Multicenter	Non-invasive+invasive	338	Quellung	74.0%	87.9%	87.9%
	Ma X[101]	2006-2008	<14 y	Multicenter	invasive	171	Quellung	63.2%	80.7%	80.7%
	Zhang YJ[102]	2007-2011	All age	Multicenter	Non-invasive+invasive	39	Quellung	64.1%	87.2%	89.7%
	Chen C[103]	2008-2010	unknown	Multicenter	Non-invasive+invasive	277	Quellung	45.5%	51.6%	64.6%
	Wang Q[104]	2010-2011	All age	Multicenter	Non-invasive+invasive	471	Quellung	39.1%	67.5%	62.6%

Notes: [a]Vaccine Coverage Rate was calculated as the percentage of isolates from each study that belonged to the serogroups/serotypes included in the PCVs.

south region than in north region, though fewer strains of serotype 6A in south region. (Table 2).

During 1996–1999, the most prevalent serotypes/serogroups were 23F, 6A, 19F, 14, and 6B; during 2005–2009 and 2010–2016, the most prevalent serotypes/serogroups were 19F, 19A, 23F, 14, and 6B. The major changes were the increased frequency of serotype 19A and 19F since 2000–2004. Fig. 3 shows the distribution of vaccine serotypes of pneumococcal isolates from 1996 to 2016 in mainland China.

The range of pooled coverage for PCV10 serotypes was from 29.7% to 62.3%, that for PCV13 was 43.2%–61.4%, and that for PPSV23 was 50.7%–65.5%, depending on different age groups. For different sources, the pooled coverage for PCV10 serotypes ranged from 43.2% to 61.4%, that for PCV13 ranged from 55.7% to 87.4%, and that for PPSV23 ranged from 62.8% to 86.9%. Regarding to different regions, the pooled coverage for PCV10 serotypes varied from 36.3% to 50.1%, that for PCV13 varied from 50.5% to 64.5%, and that for PPSV23 varied from 47.8% to 62.8%. (Table 2) Before 2004, the pooled coverage rates for vaccines serotypes were very low, which were 24.9% (95% CI: 14.8%–35.0%) for PCV10 serotypes, 29.6% (95% CI: 16.2%–43.0%) for PCV13 and 27.1% (95% CI: 15.8%–38.4%) for PPSV23. Since 2005, the pooled coverage for vaccines

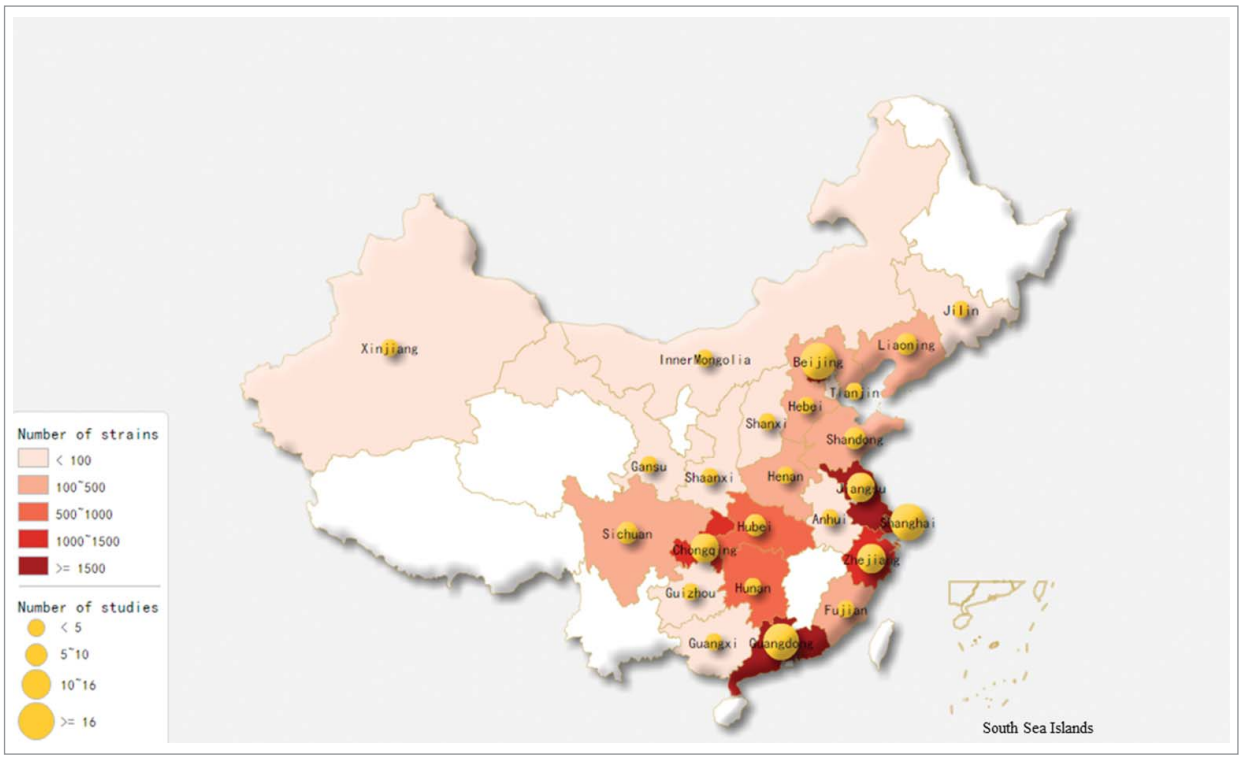

Figure 2. The regional distribution of enrolled studies and pneumococcal isolates.

Table 2. Serotype distribution and vaccine-serotype coverage of the pneumococci isolated from 2000 to 2016 in mainland China.

Strains	Serotype /Serogroup	Number (n)	Proportion (%)	95% CI	I^2(%) [a]	P [b]
Strains from children<18y (N = 11,711)						
	19F	3487	29.8	28.3–30.0	/	/
	19A	1192	10.2	9.3–10.4	/	/
	23F	1089	9.3	8.6–9.7	/	/
	14	859	7.3	7.9–8.9	/	/
	6B	581	5.0	6.8–7.7	/	/
	6A	500	4.3	3.9–4.6	/	/
	19	446	3.8	3.5–4.2	/	/
	23	280	2.4	2.1–2.7	/	/
	6	277	2.4	2.1–2.6	/	/
	15	207	1.8	1.5–2.0	/	/
	PCV10	/	52.3	44.3–60.3	99.1	<0.001
	PCV13	/	68.4	60.8–76.	99.5	<0.001
	PPSV23	/	65.5	58.0–73.0	99.4	<0.001
Strains from adults≥18y (N = 1,963)						
	19	248	12.6	11.2–14.1	/	/
	3	242	12.3	10.9–13.8	/	/
	6	178	9.1	7.8–10.3	/	/
	19F	172	8.8	7.5–10.0	/	/
	23	146	7.4	6.3–8.6	/	/
	19A	122	6.2	5.1–7.3	/	/
	14	106	5.4	4.4–6.4	/	/
	23F	71	3.6	2.8–4.4	/	/
	15	52	2.6	1.9–3.4	/	/
	17	25	1.3	0.8–1.8	/	/
	PCV10	/	29.7	19.2–40.3	97.0	<0.001
	PCV13	/	49.5	32.6–66.3	98.6	<0.001
	PPSV23	/	50.7	34.6–66.9	98.3	<0.001
Invasive strains (N = 896)						
	19F	210	23.5	20.6–26.3	/	/
	19A	201	22.2	19.4–25.0	/	/
	14	146	16.4	13.9–18.9	/	/
	23F	59	6.7	5.0–8.4	/	/
	6B	44	5.1	3.6–6.6	/	/
	9V	32	3.6	2.4–4.8	/	/
	1	17	1.9	1.0–2.8	/	/
	8	15	1.7	0.8–2.5	/	/
	7F	13	1.5	0.7–2.2	/	/
	5	10	1.1	0.4–1.8	/	/
	PCV10	/	61.4	55.2–67.7	70.6	<0.001
	PCV13	/	87.4	82.7–92.0	79.4	<0.001
	PPSV23	/	86.9	81.7–92.2	84.6	<0.001
Non-invasive strains (N = 7,577)						
	19F	2,006	26.5	25.5–27.5	/	/
	19A	637	8.4	7.8–9.0	/	/
	23F	600	7.9	7.3–8.5	/	/
	14	499	6.6	6.0–7.1	/	/
	19	439	5.8	5.3–6.3	/	/
	6A	371	4.9	4.4–5.4	/	/
	6B	350	4.6	4.1–5.1	/	/
	23	299	3.9	3.5–4.4	/	/
	6	241	3.2	2.8–3.6	/	/
	15	171	2.3	1.9–2.6	/	/
	PCV10	/	43.2	33.2–53.2	99.4	<0.001
	PCV13	/	55.7	43.5–67.8	99.7	<0.001
	PPSV23	/	53.4	41.5–65.3	99.7	<0.001
Strains from the south of China(N = 9,442)						
	19F	2452	26.0	25.1 -26.9	/	/
	19A	852	9.0	8.4 -9.6	/	/
	23F	811	8.6	8.0 -9.2	/	/
	19	747	7.9	7.4–8.5	/	/
	14	609	6.4	6.0–6.9	/	/
	6B	452	4.8	4.4–5.2	/	/
	6	382	4.0	3.6–4.4	/	/
	6A	348	3.7	3.3–4.1	/	/
	23	312	3.3	2.9–3.7	/	/
	3	237	2.5	2.2–2.8	/	/
	PCV10	/	50.1	40.5–59.6	98.2	<0.001
	PCV13	/	64.5	54.8–74.2	99.3	<0.001
	PPSV23	/	62.8	53.2–72.4	98.7	<0.001

(*Continued on next page*)

Table 2. (*Continued*)

Strains	Serotype /Serogroup	Number (n)	Proportion (%)	95% CI	I^2(%) [a]	P [b]
Strains from the north of China (N = 3,608)						
	19F	508	14.1	12.9–15.2	/	/
	23F	343	9.5	8.5–10.5	/	/
	19	289	8.0	7.1–8.9	/	/
	14	264	7.3	6.5–8.2	/	/
	6A	233	6.5	5.7–7.3	/	/
	19A	191	5.3	4.6–6.0	/	/
	23	143	4.0	3.3–4.6	/	/
	6	113	3.1	2.6–3.7	/	/
	6B	105	2.9	2.4–3.5	/	/
	15	92	2.5	2.0–3.1	/	/
	PCV10	/	36.3	26.7–45.9	98.2	<0.001
	PCV13	/	50.5	36.2–64.8	99.3	<0.001
	PPSV23	/	47.8	35.7–59.9	98.7	<0.001

Notes:

[a]I^2 means the total variation across studies that were due to heterogeneity.

[b]P: The Cochran chi-square (χ^2) test of Heterogeneity. A P value of <0.05 was considered statistically significant.

/: Not applicable.

serotypes increased gradually. During 2010–2016, the pooled coverage for PCV10 serotypes was 54.4% (95% CI: 46.5%–62.3%), that for PCV13 was 73.3% (95% CI: 67.8%–78.8%) and that for PPSV23 was 71.6% (95% CI: 65.9%–77.2%). (Fig. 3)

Heterogeneity and meta-regression

We noticed high heterogeneity between studies (I^2 = 70.6%–99.7%) (Table 2). We performed meta- regression analysis and used variables, including age (<18 y vs ≥18 y) region (northern vs southern), source (invasive vs non-invasive), serotype method (PCR vs Quellung), number of strains, and study year. In univariate analysis, we noticed that regions ($p = 0.003$) and study year ($p = 0.016$) were associated with the coverage rate of PCV13 serotypes. However, in multivariable analysis, regions, sources and study years explained 41% of the total heterogeneity. (Table 3)

Discussion

Of the currently available data from the published papers, serotype 19F pneumococcus was the most common cause of invasive and non-invasive pneumococcal disease (PD) in mainland China, followed by serotype 19A pneumococcus. Among children aged <18 years, serotype 19F pneumococcus was the main cause of IPD, a finding that was different from Johnson's finding that serotype 14 pneumococcus was the most common cause of IPD in Africa, Asia, Europe, and North America etc.[8] Thus, the most common serotypes causing IPD may vary slightly across geographic regions.

Among the strains isolated from children aged younger than 18 years, serotypes 19F, 19A and 23F were the most common serotypes, results that were similar to those of Lyu et al.[7] In addition, serotype 23F, 14 and 6B were important causes of either PD or IPD in children. This finding was consistent with the results from Western Europe and the USA that serogroups 14, 23, and 6 were common serogroups.[9] However, among the strains isolated from adults, the most common serotypes/serogroups were 19, followed by 3, and 6. Similarly, several studies in Asia reported that the prevalence of serotype 3 increased from 14.3% to 24.3% in adults and even became the most prevalent among patients aged older than 65 years.[10,11] Thus, the prevalent serotypes may vary among age groups. The most prevalent serotypes were similar in the north and south, and serotype/serogroup 19F (or 19) was the most frequent in the various regions, though the rate of each serotype is

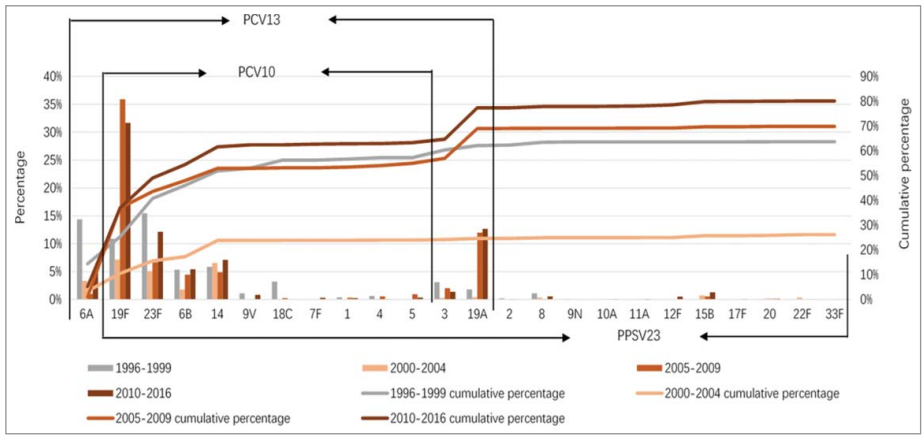

Figure 3. Distribution of vaccine serotypes of pneumococcal isolates from 1996 to 2016 in mainland China.

Table 3. Results of Meta-regression for pneumococcal serotype coverage of PCV13 in mainland China from 2000 to 2016.

Covariate[a]	Meta-regression Coefficient	95% Confidence Interval	P value	Adj R-squared[b]
Univariate analyses				
Age (<18y vs ≥18y)	−0.268	−0.944 to 0.407	0.427	−0.92%
Region (northern vs southern)	0.355	0.133 to 0.578	0.003	25.37%
Source (invasive vs non-invasive)	0.273	−0.142 to 0.689	0.188	2.82%
Serotype (PCR vs Quellung)	−0.077	−0.399 to 0.246	0.629	−2.70%
Number of strains	0.000	−0.001 to 0.001	0.663	−2.13%
Study year	−0.515	−0.865to −0.166	0.005	35.80%
Multivariable analyses				41.18%
Age (<18y vs ≥18y)	0.076	−0.474 to 0.626	0.780	
Region (northern vs southern)	0.345	0.174 to 0.516	<0.001	
Source (invasive vs non-invasive)	0.331	0.021 to 0.641	0.037	
Serotype (PCR vs Quellung)	−0.142	−0.385 to 0.100	0.241	
Number of strains	0.001	−0.000 to 0.001	0.092	
Study year	−0.370	−0.665 to -0.076	0.016	

Notes: [a]The dependent variance of the Meta-regression was the serotype coverage rate (r) of PCV13. The covariates included in the univariate and multivariable models were age (<18 y vs ≥18y), region (northern vs southern), source (invasive vs non-invasive), serotype (PCR vs Quellung), number of strains, and study year.
[b]Adj R-squared was the proportion of variance that can be explained.

different. Additionally, serotype19A is more frequent in the south than in the north. Thus, the serotypes of *S. pneumonia* vary in different areas.

For all of the isolates included in our study, the coverage rates of PCV13 and PPSV23 were significantly higher than those of PCV10, with no significant differences between PCV13 and PPSV23, a finding that was s consistent with other study findings in China.[7,12] Although the number of serotypes in PPSV23 was more than that in PCV13, the serotype coverage of PPSV23 was slightly lower than that of PCV13, potentially due to the lack of serotype 6A in PPSV23 and the contribution of serotype 6A is higher than the combined contribution of the 11 serotypes unique to PPSV23. PCV13 has higher coverage compared with PCV7,[13] and the additional serotypes 1, 5, 7F, 3, 6A and 19A, especially for serotype 19A, account for a large proportion. In our study, PCVs or PPSV coverage among children was higher than that among adults, consistent with the results of a study from China.[14] Among the isolates from children, PCVs or PPSV coverage of invasive isolates was higher than that of non-invasive isolates. In the USA, the rate of IPD reduced dramatically after 5 years since the license of PCV13, especially driven by decreases in 19A.[15] Considering the comprehensive evidence concerning the effectiveness of PCV13 we could expect a similar reduction of IPD if we have a high vaccination rate of PCV13 in mainland China.

In mainland China, PCV7 was licensed since 2008 and PCV13 was licensed since 2016, but both as self-paid vaccine and the extent of adoption was very low. Thus the natural fluctuation in serotype distribution in China for the last 20 years appears to not have significantly influenced from PCVs introductions. The major changes were the increasing of serotype 19A and 19F since 2000–2004, which may have been mainly due to the selective pressure of antibiotics usage. In the USA, the non-PCV7 serotype 19A increased in prevalence from 2.7% in 1999–2000 to 34.1% in 2010–2011 after 10 years of PCV7 licensed, but these serotype fluctuations have been mainly attributed to serotype replacement following PCV7 immunization.[16,17]

In other countries, serotype shift is a phenomenon since the use of PCV7.[13,14] Although PCV7 is not widely used in China, the increasing of serotype19A was obvious since 2000, and serotype 19A is one of the most common serotypes in most areas of China.[15] The serotype shift in China may be due to the selective pressure of antibiotics rather than the use of PCV7, because of the antibiotics were commonly used in China. In the future, we need to keep monitoring the serotype distribution and change.

There are some limitations in this systematic review and meta-analysis. First, we used different thresholds for a number of invasive (>30) and of non-invasive isolates (>40), which might lead to some bias. In consideration of the common usage of antibiotics, lower bacterial load and the quality of the specimens, it's more difficult to isolate the invasive pneumococcal strains in the fields, but the invasive pneumococcal diseases are more severe than non-invasive pneumococcal diseases. Therefore, we used a lower threshold for invasive isolates to include more meaningful data in this meta-analysis. Second, we observed large heterogeneity of the included articles, but regions, sources, and study years only explained part of the observed heterogeneity, other possible reasons remain unknown. Third, serotype coverage of vaccines may be underestimated in our study, because only serotypes were used in the pooled coverage regardless of serogroup data. Furthermore, most of the included studies came from southeastern of mainland China; few came from northwestern provinces, such as Xinjiang, Qinghai and Ningxia province. To better understand the impact of PCV13 on these areas, more data are needed.

In conclusion, pneumococcal serotype 19F was the most prevalent serotype in mainland China, and the most common serotypes varied among the population, between invasive and non-invasive isolates, and across geographic regions. The serotype coverage rates of PCV13 and PPSV23 were high in mainland China. During and after the introduction of PCV13 in China, more scientific data are required, especially from northwestern China; the serotype distribution should be monitored over an extended time period.

Methods

Literature search

A systematic literature search was conducted in PubMed, Ovid-EMBASE, Web of Science, CNKI, and Wanfang. We searched electronic medical databases for studies (published between January 1, 2000 and December 31, 2016) reporting pneumococcal serotypes from hospitalization patients or isolates from healthy people in mainland China. Strategies were designed to retrieve records that included the following terms: ("*Streptococcus pneumoniae*" OR "*S. pneumoniae*" OR "pneumococcus" OR "pneumococci" OR "diplococcus pneumoniae" OR "diplococcus" OR "pneumococcal") and ("serotype" OR "serotypes" OR "serogroups" OR "serogroup") and ("China" OR "Chinese")

Criteria for selection

We included an article if (1) It was an original study, and the isolates were serotyped by multiplex polymerase chain reaction or capsular Quelling reaction methods; (2) the number of isolates was ≥30 for invasive isolates or ≥ 40 for non-invasive isolates; and (3) the strains were isolated from the population in mainland China (except Hong Kong, Macao and Taiwan). We excluded an article if (1) it was a review, case report or lecture; (2) it lack a detailed description about the serotypes of the isolates; (3) it was a duplicate publication. For more detailed information, please refer to Fig. 1.

Data extraction

The following information was extracted from each selected paper: first author's name, study region, age of study population, source of isolates, years of isolates collected, number of isolates, and the serotypes.

Invasive pneumococcal isolates were defined as *S. pneumoniae* strains identified from a normally sterile site (e.g., blood, cerebrospinal, pleural effusions, or joint fluid, etc.). Non-invasive pneumococcal strains were defined as *S. pneumoniae* strains isolated from non-sterile sites such as sputum or middle ear effusion. Vaccine serotypes referring to the serotypes included in the pneumococcal conjugate vaccines or pneumococcal polyvalent vaccine (details in Box 1).

Box 1. Serotypes in Pneumococcal conjugate vaccines or polysaccharide vaccine

PCV7	4 6B 9V 14 18C 19F 23F
PCV10	4 6B 9V 14 18C 19F 23F 1 5 7F
PCV13	4 6B 9V 14 18C 19F 23F 1 5 7F 3 19A 6A
PPSV23	4 6B 9V 14 18C 19F 23F 1 5 7F 3 19A 2 8 9N 10A 11A 12F 15B 17F 20 22F 33F

Data analysis

The collected isolates were stratified by the properties of each study into children or adults, invasive isolates or non-invasive isolates, southern or northern regions. Southern or northern regions were defined by Qinling Mountains and Huai River.

I^2 was used to describe the percentage of the total variation across studies that were due to heterogeneity. $I^2 = 25\%$ was associated with low heterogeneity, $I^2 = 50\%$ was associated with moderate heterogeneity, and $I^2 = 75\%$ was associated with high heterogeneity.[18] Two-sided $p \leq 0.05$ was considered statistically significant.[19] Most of our meta-analysis, showed high heterogeneity (I^2>75%). Considering the high heterogeneity among studies, we used the random-effects models for the pooled estimation of the serotype coverage rate of PCVs.

To explore which study characteristics explained the large heterogeneity, meta-regression was conducted according to potentially relevant characteristics.

The PCV serotype coverage rate (r) was calculated as the total number of isolates included in the vaccine serotypes divided by the total number of isolates that were serotyped. The standard error (SE) of the coverage rate was calculated as SE = Sqr(r*(1-r)/n). The coverage rate of PCVs from different studies were pooled with using the random-effects model.

All statistical analyses were performed using Stata SE 12.0 (Stata Corp, College Station, TX).

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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References

1. He C, Kang L, Miao L, Li Q, Liang J, Li X, Wang Y, Zhu J. Pneumonia Mortality among Children under 5 in China from 1996 to 2013: An Analysis from National Surveillance System. PLoS One. 2015;10(7):e0133620. doi:10.1371/journal.pone.0133620. PMID:26186717.
2. Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, O'Brien KL, Campbell H, Black RE. Global burden of childhood pneumonia and diarrhoea. Lancet. 2013;381(9875):1405–16. doi:10.1016/S0140-6736(13)60222-6. PMID:23582727.
3. O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, Lee E, Mulholland K, Levine OS, Cherian T. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet. 2009;374(9693):893–902. doi:10.1016/S0140-6736(09)61204-6. PMID:19748398.
4. Organization WH. Estimated Hib and Pneumococcal Deaths for Children Under 5 Years of Age, 2008. 2013.
5. Balsells E, Guillot L, Nair H, Kyaw MH. Serotype distribution of Streptococcus pneumoniae causing invasive disease in children in the post-PCV era: A systematic review and meta-analysis. PLOS ONE. 2017;12(5):e0177113. doi:10.1371/journal.pone.0177113. PMID:28486544.
6. World Health Organization [WHO]; United Nations Children's Fund [UNICEF. Ending preventable child deaths from pneumonia and diarrhoea by 2025. The integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD).[J]. Geneva Switzerland Who, 2013.
7. Lyu S, Hu HL, Yang YH, Yao KH. A systematic review about Streptococcus Pneumoniae serotype distribution in children in mainland of China before the PCV13 was licensed. Expert Rev Vaccines. 2017;16(10):1–10.

8. Johnson HL, Deloria-Knoll M, Levine OS, Stoszek SK, Freimanis HL, Reithinger R, Muenz LR, O'Brien KL. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. PLoS Med. 2010;7 (10):e1000348. doi:10.1371/journal.pmed.1000348. PMID:20957191
9. Hausdorff WP, Siber G, Paradiso PR. Geographical differences in invasive pneumococcal disease rates and serotype frequency in young children. Lancet. 2001; 357:950–2. doi:10.1016/S0140-6736 (00)04222-7. PMID:11289365.
10. Kawaguchiya M, Urushibara N, Aung MS, Shinagawa M, Takahashi S, Kobayashi N. Serotype distribution, antimicrobial resistance and prevalence of pilus islets in pneumococci following the use of conjugate vaccines. J Med Microbiol. 2017;66(5):643–650. doi:10.1099/jmm.0.000479. PMID:28516842.
11. Miyazaki H, Shibuya R, Midorikawa N, Chang B, Ohnishi M, Matsumoto T. Serotype distribution and antimicrobial susceptibility of Streptococcus pneumoniae strains isolated in Japan after introduction of the routine immunization program. J Infect Chemother. 2017;23(4):234–240. doi:10.1016/j.jiac.2016.12.016. PMID:28161295.
12. Yao KH, Yang YH. Streptococcus pneumoniae diseases in Chinese children: past, present and future. Vaccine. 2008;26(35):4425–33.1999-2011(1.). Emerg Infect Dis. 2013 Jul;19(7):1074-83. doi:10.1016/j.vaccine.2008.06.052. PMID:18602435.
13. Eliakim M, Levy M, Ehrenfeld M, Reimann HA. Resurgence of the multiresistant pneumococcus in the United States: a commentary. Pediatr Infect Dis J. 2007;26(6):473–474. doi:10.1097/INF.0b013e3180517b8b. PMID:17529861.
14. Kaplan SL, Barson WJ, Lin PL, Stovall SH, Bradley JS, Tan TQ, Hoffman JA, Givner LB, Mason EOJ. Serotype 19A is the most common serotype causing invasive pneumococcal infections in children. Pediatrics. 2010;125(3):429. doi:10.1542/peds.2008-1702. PMID:20176669.
15. Balsells E, Guillot L, Nair H, Kyaw MH. Serotype distribution of Streptococcus pneumoniae causing invasive disease in children in the post-PCV era: A systematic review and meta-analysis. PLOS ONE. 2017;12(5):e0177113. doi:10.1371/journal.pone.0177113. PMID:28486544.
16. Butler JC. Epidemiology of pneumococcal serotypes and conjugate vaccine formulations. Microb Drug Resist. 1997 Summer;3(2):125–9. doi:10.1089/mdr.1997.3.125.
17. Sandra S. Richter, Kristopher P. Heilmann, Cassie L. Dohrn, Fatholllah Riahi, Daniel J. Diekema, Gary V. Doern. Pneumococcal serotypes before and after introduction of conjugate vaccines, United States 1999-2011[1]. Emerg Infect Dis. 2013;19(7):1074–83. doi:10.3201/eid1907.121830.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. British Medical Journal. 2003;327 (7414):557–560. doi:10.1136/bmj.327.7414.557. PMID:12958120.
19. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. Journal of Clinical Epidemiology. 2000;53(11):1119–1129.
* Reference of included publications showed in Talbe1: doi:10.1016/S0895-4356(00)00242-0. PMID:11106885.
20. Yang F, Zhang YY. Drug resistance of Streptococcus pneumoniae isolated from respiratory tract infection. Chinese Journal of anti infection chemotherapy. 2001;1(01):13–16..
21. Yang F, Zhang YY, Lesley M, Avril W, Keith K, Wu WH, Zhou L, Zhu DM, Wang F. Population biology of Streptococcus pneumoniae carried by healthy children in Shanghai. Natl Med J China. 2001;81 (10):16–19
22. Li ZF, Pan SG, Li HW. Drug resistance and serological characteristics of Streptococcus pneumoniae in children. Practical Preventive Medicine. 2002;9(02):115–118.
23. Zhao GM, Black S, Shinefield H, Wang CQ, Zhang YH. Serotype distribution and antimicrobial resistance patterns in Streptococcus pneumoniae isolates from hospitalized pediatric patients with respiratory infe… Pediatric Infectious Disease Journal. 2003;22(8):739–742. doi:10.1097/01.inf.0000078373.54515.40. PMID:12913778.
24 Wang CQ, Wang AM, Zhang YH, Zhao GM, Wang DM. Serotyping and resistance of streptococcus pneumoniae isolates from children with respiratory tract infection. Chinese Journal of Infection and Chemotherapy. 2002;2(04):218–220.
25. Wang CQ, Wang DM, Wang AM. Study on drug resistance of respiratory tract pathogens in 2000∼2002 years. Chinese Journal of laboratory medicine. 2004, 27(2):114–116.
26. Luo XM, Gu YC, Liang JP, Gao SZ, Li ZQ, Zhou RD. Investigation of drug resistance and serotype distribution of Streptococcus pneumoniae. Practical preventive medicine. 2003;10(06):835–837.
27. Zhang ZY, Zhang J, Li L, Zhu XH, Wang HW, Ma Y. Epidemiological study of streptoccoccus pneumoniae in the nasopharynx of healthy children under 5 years of age in Wuhan. Chinese Journal of Pediatrics. 2007;45(05):382–386.
28. Zhang J, Sun ZY, Ma Y, Li JY, Jin SH. Resistance and Serotype of 152 Strains of Streptococcus pneumoniae. Chin J N osocomiol. 2007;17 (04):468–471.
29. Zhang J, Sun ZY. Population biology of streptococcus pneumoniae carried by healthy children. Chinese Journal of Infection and Chemotherapy. 2007;7(02):96–100.
30. Liu YK. Study on the Serotyping and Resistance to erythromycin of Streptococcus pneumoniae in Wuhan. Journal of Xiangnan University(Medical Sciences). 2006;8(03):4−6+9.
31 Yang F, Xu XG, Yang MJ, Zhang YY, Klugman KP, McGee L. Antimicrobial susceptibility and molecular epidemiology of Streptococcus pneumoniae isolated from Shanghai, China. Int J Antimicrob Agents. 2008;32(5):386–91. doi:10.1016/j.ijantimicag.2008.05.004. PMID:18723327.
32. Ren HY, Wang XL, Li MC, Zhang L, Gao Y, Shao ZJ. Resistance and Serotype of 123 Strains of Streptococcus Pneumoniae. Chinese Journal oF Vaccines and Immunization. 2010;16(01):52–55.
33. Zhang XH, Serotype/serogroup distribution of Streptococcus pneumoniae isolated from clinical patients and surveillance on antimicrobial resistance in 2004—2009, Drug Evaluation Research. 2011;34(02):101–104.
34. Pan W, Yue YL. Serotype distribution and drug resistance of children with invasive Streptococcus pneumoniae in Nanjing. Zhejiang Clin Med J. 2014;16(11):1811–1812.
35. Yang T, Li BS, Ke BX, Zeng HH, Peng TH, Ke CW, Wang JJ. Serological typing of Streptococcus pneumoniae clinical isolates from 2005 to 2013 in Guangdong Province. Guangdong Medical Journal. 2015;36(16):2568–2570.
36. Zhao RZ, Zheng YJ, Deng QL, Wang HM, Chen Q, Deng JG. Serotype / serogroup distribution and antimicrobial resistance of Streptococcus pneumoniae in children with community—acquired pneumonia in Shenzhen area. Chin J Infect Chemother. 2010;10 (03):205–208.
37. Deng QL, Deng L, Hhuang XQ, Xie YQ, Huang Y, Zhou ZW, Yu JL, Zhao CA. Serotype Distribution and Antibiotic Resistance of Streptococcus pneumoniae Isolated from Children in Guangzhou. Journal of Tropical Medicine. 2008;8(11):1130–1133.
38. Dong YS, Huang WX, Zhang C, Luo T, Zhu WM, Li CZ, Zhang XP. Resistance and serotype of Streptococcus pneumoniae isolated from clinical patients in Chongqing. Chinese Journal of antibiotics. 2010;35(01):59–64.
39. Dong YS, Huang WX, Luo T, Zhang C, Wu LX. Prevalence of virulence genes in Streptococcus pneumoniae straias isolated from clinical patients. Chin J Microbiol Immunol. 2009;29(2):177–180.
40. Zhang H, Li WH, Kong J, Wang C, Lu M, Lu Q. Serotype distribution and antimicrobial resistance of Streptococcus pneumoniae isolated from the children in Shanghai. Chin J Infect Chemother. 2011;11(04):287–290.
41. Xu F, Chi FL, Tan H, Liu XM, Cao T, Pan W, Zhong TY. Study on serotype distribution in 48 isolates of invasive Streptococcus pneumoniae with which children infected. Chinese Journal of biochemical medicine. 2012;33(06):909−910+912.
42. Miao DQ, Xu F, Li JQ, Liu JJ, Shao ZQ, Zhu T, Zhong TY. Serotype distribution of streptococcus pneumoniae from children's clinical isolates in Nanjing. China Medical Engineering. 2016;24(02):12–15

43. Hu, J., Sun, X., Huang, Z., Wagner, A. L., Carlson, B., & Yang, J., Tang S, Li Y, Boulton ML, Yuan Z. (2016). Streptococcus pneumoniae and haemophilus influenzae type b carriage in chinese children aged 12–18 months in shanghai, china: a cross-sectional study. Bmc Infectious Diseases, 16(1), 149. doi:10.1186/s12879-016-1485-3. PMID:27080523.
44. Zhao DF, Hu Q, Xiong Y, Quan YX, Ai YS, Wang JK. Study on the carrying rate and serotype distribution of streptococcus pneumoniae of healthy infants in Wuhan. Modern Preventive Medicine. 2012;39 (09):2166–2168.
45. Zhang C, Dong YS, Huang WX. Streptococcus pneumonia distributed in different serotypes isolated from children and adults, and their antibiotic sensitivity:A study in Zigong, Sichuan. Journal of practical hospital clinical. 2012;9(01):82–85.
46. Li JP, Ye Q, Shrn YF, Lou YF, Chrn XJ, Hhua CZ, Shang SQ, Chen ZM. Drug resistance and serotype of Streptococcus pneumoniae in children's Hospital of Zhejiang University in 2009～2010. Chinese Journal of Pharmaceuticals. 2012;47(10):792–795.
47. Ying QH, Yang L, Ding JL, Song XH, Ma YY, Du W. Serotype distribution and antimicrobial resistance patterns of Streptococcus pneumoniae isolates in Shaoxing area. Chinese Journal of Health Laboratory Technology. 2012;22(01):155–157.
48. Zhang B, Gertz R, Liu Z, Li Z, Fu W, Beall B. Characterization of highly antimicrobial-resistant clinical pneumococcal isolates recovered in a Chinese hospital during 2009 – 2010. Journal of Medical Microbiology. 2012;61: 42–48. doi:10.1099/jmm.0.035675-0.
49. Chen DL, Li MC, Zhou HJ, Liu GJ, Wang Y, Yu BQ, Shi MM, Chen XF, Hong Y. Study of molecular of 80 clinical streptococcus pneumoniae strains in Maanshan area. Chinese Journal of Preventive Medicine. 2015;49(1):56–59. PMID:25876497.
50. Ma X., Zhao R., Ma Z., Yao KH., Yu S, Zheng, Y., Yang Y. Serotype distribution and antimicrobial resistance of streptococcus pneumoniae isolates causing invasive diseases from shenzhen children's hospital. Plos One. 2013;8(6), e67507. doi:10.1371/journal.pone.0067507. PMID:23840728.
51. Lin XF, Liu CX, Yang HW, Li FQ, Li XY, Yang JH. Study of serotype distribution and antimicrobial resistance in 52 isolates of invasive Streptococcus pneumoniae. Chin J Health Lab Tec. 2015;25(02):281–283.
52. Zhou K, Xie GJ, Wang XW, Xu F, Yao KH. Clinical characteristics and serotype distribution of invasive pneumococcal disease. Chinese Journal of hospital infection. 2015;25(15):3392–3394.
53. Jing CM, Wang C Resistance and serotype of Streptococcus pneumoniae isolates from children in Chongqing from 2009 to 2014, Chinese Journal of antibiotics. 2016;41(01):64–69.
54. Kang LH, Liu MJ, Xu WC, Cui JJ, Zhang XM. Molecular epidemiology of pneumococcal isolates from children in China. Saudi Medical Journal. 2016;37(4):403–13. doi:10.15537/smj.2016.4.14507. PMID:27052283
55. Lu C. Investigation of serotype distribution of invasive Streptococcus pneumoniae in children. International Journal of Laboratory Medicine. 2015;36(07):990–992.
56. Liu MJ, Zhang Q, Wang H. Analysis for serotypes of 46 strains of invasive Streptococcus pneumoniae and their conservation of virulence factors. Chin J Clin Lab Sci. 2013;31(12):934–937.
57. Song XQ, Duan DR, Lan JX. Serotype and drug resistance of Streptococcus pneumoniae from preschool children with suppurative otitis media. Chinese Journal of Microecology. 2015;27(07):819–823.
58. Li M, Tan DD, Zhang QT, Zhou Y, Li W, Guo WT, Guo JJ. Seotype distribution and antimicrobial resistance of streptococcus pneumoniae in children in humen area. Chinese Journal of infection and chemotherapy. 2015;15(01):43–46.
59. Huang S, Liu X, Lao W, Zeng S, Liang H, Zhong R, Dai X, Wu X, Li H, Yao Y. Serotype distribution and antibiotic resistance of Streptococcus pneumoniae isolates collected at a Chinese hospital from 2011 to 2013. BMC Infectious Diseases. 2015;15(1):312. doi:10.1186/s12879-015-1042-5.
60. Ding Y, Geng Q, Tao Y, Lin Y, Wang Y. Etiology and Epidemiology of Children With Acute Otitis Media and Spontaneous Otorrhea in Suzhou, China. Pediatric Infectious Disease Journal. 2015;34:e102–e106. doi:10.1097/INF.0000000000000617. PMID:25379833
61. Jiang HQ, Chen ML, Li TM, Tian YR, Zhu YJ, Liu H, Li M. Molecular characteristics of Streptococcus pneumoniae in Shanghai, China. Chin J Lab Med. 2015;38(4):256–261.
62. Wang J, Liu F, Ao P, Li X, Zheng H. Detection of Serotype Distribution and Drug Resistance of Streptococcus Pneumoniae Isolated From Pediatric Patients. Laboratory Medicine. 2016;48(1):39–45.
63. Wang LM, Wu JQ, Fang YF. Epidemiological characteristics and drug resistance changes of Streptococcus pneumoniae in lower respiratory tract infection of preschool children. Chin J Health Lab Tec. 2016;26(09):1349–1352.
64. Li ST, Yue YL, Sun H, Tang YY, Chen HB, Serotype / serogroup distribution of Streptococcus pneumoniae isolated from sputum of 584 clinical isolates of children Int J Lab Med, September 2014;35(18):2565–2566.
65. Pan F, Han L, Kong J, Wang C, Qin H, Xiao S, Zhu J, Zhang H. Serotype distribution and antimicrobial resistance of Streptococcus pneumoniae causing noninvasive diseases in a Children's Hospital, Shanghai. The Brazilian Journal of Infectious Diseases. 2015;19(2):141–145. doi:10.1016/j.bjid.2014.08.010. PMID:25636183.
66. Huang LH, Yuan YT, Wang YF, Zhang JM, Zhang J, Huang JW. Clinical characteristics, serotype and drug resistance of 265 clinical isolates of Streptococcus pneumoniae. Fujian Medical Journal. 2015;37(03):78–81.
67. Geng Q, Zhang T, Ding Y, Tao Y, Lin Y, Wang Y, Black S, Zhao G. Molecular characterization and antimicrobial susceptibility of Streptococcus pneumoniae isolated from children hospitalized with respiratory infections in Suzhou, China. PLoS One. 2014;9:e93752.. doi:10.1371/journal.pone.0093752. PMID:24710108.
68. Pan F, Han L, Huang W, Tang J, Xiao S, Wang C, Qin H, Zhang H. Serotype Distribution, Antimicrobial Susceptibility, and Molecular Epidemiology of Streptococcus pneumoniae Isolated from Children in Shanghai, China. PLOS ONE. 2015;10(11):e0142892. doi:10.1371/journal.pone.0142892. PMID:26571373.
69. Chen CZ, Shi W, Peng YJ, Xiong W, Yuan L, Gao W, Cheng XP, Yao KH. Nasopharyngeal carriage rate, serotype distribution and antibiotic resistance pattern of streptococcus pneumoniae isolates collected from hospitalized children with respiratory tract infections in a single center grade two hospital in western of china: a cross -sectional study. Chinese Journal of Evidence Based Pediatrics. 2016;11(4):241–246.
70. Yu SJ, Wang JF, Li J, Li Y, Wang XL, Whitney CG, Levine OS, Dowell SF, Yang YH. Resistance, serotypes and "hidden resistant clones" of Streptococcu pneumoniae among children in Beijing. Chin J Pediatr. 2000;38(07):23–26.
71. Lesley M, Wang H, Avril W, Robin H, Chen M, Klugman KP. Prevalence of SerotypesMolecular Epidemiology of Streptococcus pneumoniae Strains Isolated from Children in Beijing, China: Identification of Two Novel Multiply-Resistant Clones. Microbial Drug Resistance. 2001;7(1):55.
72. Li J, Yuan L, Yu S, Yang Y. Nasal carriage of Streptococcus pneumoniae among children in Beijing. Chin Med J (Engl). 2001;114 (11):1196–200. PMID:11729519.
73. Yao KH, Yu SJ, Shen XZ. Serotype distribution and homology of penicillin insensitive Streptococcus pneumoniae in children from 2000 to 2002 in Beijing. Chin J Microbiol Immunol. 2007, 27 (10):960–961.
74. Yao KH, Shen XZ, Yu SJ, Tong YJ, Gao W, Yuan L, YANG YH. The serotype distribution of penicillin-nonsusceptible streptococcus pneumoniae isolated from children with upper respiratory tract infection in Beijing. Journal of Clinical Pediatrics. 2007;25(4):306–308.
75. Yu S, Yao K, Shen X, Zhang W, Liu X, Yang Y. Serogroup distribution and antimicrobial resistance of nasopharyngeal isolates of Streptococcus pneumoniae among Beijing children with upper respiratory infections (2000–2005). European Journal of Clinical Microbiology

& Infectious Diseases. 2008;27(8):649–655. doi:10.1007/s10096-008-0481-y.
76. Tong YJ, Yao KH, Yu SJ. Serotyping / Grouping and Antimicrobial Resistance of Streptococcus Pneumoniae With Upper Respiratory Infection. Chinese Journal of Vaccines and Immunization. 2007, 13 (1):75–78.
77. Wu JX, Zhu DQ, Drug resistance and molecular epidemiology of Streptococcus pneumoniae. International Journal of Laboratory Medicine. 2012;33(3):345–347.
78. Winkler M, Ringe B, Schneider K, Maibücher A, Färber L, Wietholtz H, Manns M, Pichlmayr R. Serotypes and patterns of antibiotic resistance in strains causing invasive pneumococcal disease in children less than 5 years of age. Plos One. 2013;8(1):e54254. doi:10.1371/journal.pone.0054254. PMID:23342111.
79. Zhou L, Yu S, Gao W, Yao K, Shen A, Yang Y. Serotype distribution and antibiotic resistance of 140 pneumococcal isolates from pediatric patients with upper respiratory infections in Beijing, 2010. Vaccine. 2011;29(44):7704–7710. doi:10.1016/j.vaccine.2011.07.137. PMID:21839135.
80. Wang YW, Niu M. Serotype distribution and antimicrobial susceptibility of streptococcus pneumoniae isolated from the children in Dalian. Chinese Journal of Laboratory Diagnosis. 2014;18(11):1793–1796.
81. Dou HJ, Gu CG, Cao XH. Drug resistance and serological typing of Streptococcus pneumoniae in pediatric patients. Chinese Journal of disinfection. 2015(01):76–77.
82. LI J, Ma LJ, Shi W, Zhou L, Xu WJ, Yao KH, Wang LP. Analysis of serotypes and drug resistance of Streptococcus pneumoniae in hospitalized children. Chin J Lab Med. 2015;38(9):622–626.
83. Liu ZW. Streptococcus pneumoniae serotype and antibiotic resistance in children with respiratory tract infection. Chinese Journal of science and technology database, medical. 2015;0(31):273–273.
84. Dong F, Zhen JH, Wang Y, Xu BP, Wang Q, Liu G, Yao KH, Song WQ, Shen KL. Analysis of features of streptococcus pneumoniae isolated from the cultured bacteria sample in pediatric patients. Chinese Journal of Practical Pediatrics. 2016;31(03):201–205.
85. Lyu S, Yao K, Dong F, Xu B, Liu G, Wang Q, Shi W, Tong J, Shen K, Yang Y. Vaccine Serotypes of Streptococcus pneumoniae with High-level Antibiotic Resistance Isolated More Frequently Seven Years After the Licensure of PCV7 in Beijing. The Pediatric Infectious Disease Journal. 2016;35(3):316–321. doi:10.1097/INF.0000000000001000. PMID:26584056.
86. Yu SJ, Gao W, Shi W, Yuan L, Shen AD, Yao KH, Yang YH. Nasopharyngeal carriage rate, antimicrobial resistance and serotype distribution of Streptococcus pneumoniae among children with upper respiratory infection. Chin J Contemp Pediatr. 2014;16(10):988–992.
87. Zhou MJ, Li JJ, Zhang L, Wang H, Zhang L, Jia ZY, He BH, Su W, Zheng LW, Sun YQ. Genotyping and drug resistance of Streptococcus pneumoniae in Baoding City. J Med Pest Control. 2016;32 (08):854−856+859.
88. Wang Q, Wu J, Liu J, Dong F, Yao KH, Shen KL, Qian SY. Cliuleal features and outcomes of invasive pneumococeal disease in pediatric intensive care unit. Chinese Journal of Applied Clinical Pediatrics. 2016;31(18):1400–1404.
89. Wang JF, Huang NN, Wang GZ, Yu FQ. Drug resistance profileserotype of streptococcus of pneumoniae infected pediatric patients. Pakistan Journal of Pharmaceutical Sciences. 2016;29(4 Suppl):1457.
90. Wang YT, Guo YH, Wang XI, Jia ZY, Zhang WC, Sun YQ, He BH, Liu XL. Serotype Analysis of 43 Strains of Invasive Streptococcus pneumoniae Isolated in Hebei Province, 2014. Chinese Journal of Vaccines and Immunization. 2016;22(01):6–9.
91. Zhang M, Sun M, Chen K, Yang HX, Hou Q. Serotyping and multilocus sequence typing of Streptococcus pneumoniae in infants with ocular infections. Chin J Nosocomiol. 2016;26(14):3316–3318
92. Yao KH, Lu Q, Deng L, Yu SJ, Deng QL, Tong YJ, Gao W, Yuan L, Sheng XZ, Yang YH, serotype distribution and resisitance to β-lactams of streptococcus pnemoniae isolated from children in Beijing, Shanghai, Guangzhou, 2000–2002. CHIN J Pediatr. 2006;44 (12):928–932.
93. Li MC, Zhang Q, Ren HY, Zhou HJ, Li Q, Shao ZJ. Analysis on Pneumococcus Isolated from Part of China Using Serotype and Pulsed-Field Gel Electrophoresis. Chinese Journal of Vaccines and Immunization. 2010;16(03):265–269.
94. Li MC, Ren HY, Zhu BQ, Shao ZJ. Study on the Antibiotic Resistance and Serotype of 241 Strains of Streptococcus Pneumoniae. Chinese Journal of Vaccines and Immunization. 2013;19(04):336–340.
95. Ying QH, Yang L, Ding JL, Song XH, Ying-Ying MA, Wei DU. Serotype distribution and antimicrobial resistance patterns of Streptococcus pneumoniae isolated from children in China younger than 5 years. Chinese Journal of Health Laboratory Technology. 2012;22 (01):155–157.
96. Xiao SK, Zhao CJ, Liu CL, Wang H. Resistance and serotype distribufion of Streptococcus pneumoniae among adults and children in China. Chinese Journal of tuberculosis and respiratory. 2010;33 (8):601–607.
97. Liu CL, Zhao CJ, Liu YD, Wang H. Study of serotype distdbufion, antimicrobial resistance patterns and molecular epidemiology in 148 isolates of invasive Streptococcus pneumoniae. Chinese Medical Journal. 2010;90(22):1565–1570. PMID:20973240.
98. Zhao C, Zhang F, Chu Y, Liu Y, Cao B, Chen M, Yu Y, Liao K, Zhang L, Sun Z, et al. Phenotypic and genotypic characteristic of invasive pneumococcal isolates from both children and adult patients from a multicenter surveillance in China 2005–2011. PLoS One. 2013;8(12):e82361. doi:10.1371/journal.pone.0082361. PMID:24349263.
99. Yao KH, Wang LB, Zhao GM, Zheng YJ, Deng L, Zhao RZ, Deng QL, Hu YH, Yu SJ, Shen XZ. Study on antimicrobial resistance in different serotypes of Streptococcus pneumoniae isolated from pediatric patients hospitalized for pneumonia. J Clin Pediatr. 2009;27 (06):524−527+533.
100. Yao KH, Wang LB, Zhao GM, Zheng YJ, Deng L. Pneumococcal serotype distribution and antimicrobial resistance in Chinese children hospitalized for pneumonia. Vaccine. 2011;9(12):2296–301. doi:10.1016/j.vaccine.2011.01.027.
101. Xiang MA, Yao KH, Xie GL, Zheng YJ, Wang CQ. Characterization of erythromycin-resistant Streptococcus pneumoniae isolates causing invasive diseases in Chinese children. National Medical Journal of China. 2013;126(8):1522–7.
102. Zhang YJ, Chen YS, Wang ZW, Li YQ, Wang DX, Shang Y, Fu RR, Hu YH, Geng R, Wei LP and others. Serological and molecular capsular typing, antibiotic susceptibility and multilocus sequence typing of Streptococcus pneumoniae isolates from invasive and non-invasive infections. Chin Med J (Engl). 2013;126(12):2296–303. PMID:23786942.
103. Chen C, Xiao L, Shi JC, Wang SS, Guo SY, Ye Q. Identifcation and Serotyping Result Analysis of 277 Strains of Streptococcus Pneumoniae. Chinese Journal of Medicinal Guide. 2011;13(10):1774–1775.
104. Wang Q, Zhang FF, Zhao CJ, Chen HB, Wang ZW, Guo Y, Li HN, Wang H. Antimicrobial resistance and serotype distribufion of Streptococcus pneumoniae isolated from multicenter across China, 2010-2011. Chinese Journal of tuberculosis and respiratory, Chinese Journal of tuberculosis and respiratory. 2013;36 (2):106–112.