

Background

- Streptococcus pneumoniae* remains a leading cause of disease in children and adults.
- Serotypes evolve and differ in invasiveness, virulence and antibiotic resistance; therefore, serotype surveillance is necessary to monitor the burden of pneumococcal disease, especially in the setting of childhood pneumococcal vaccination programs with the 10- and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13).

Objective

The objective of this study was to determine the serotypes and antibiotic susceptibilities of a convenience sample of 3,997 *S. pneumoniae* isolates collected from 50 countries in seven geographic regions through the Tigecycline Evaluation Surveillance Trial, (TEST) from 2010-2015 for comparison to a previous study of 2,173 isolates collected between 2004-2009.

Methods

- Investigators enrolled in the TEST program collect clinically relevant causative agents from a variety of sterile body sites.
- Only one isolate per patient is accepted. Individual sites are requested to collect and ship a total of 15 *S. pneumoniae* isolates per year to International Health Management Associates (IHMA).
- Susceptibility testing is performed using supplied panels and standard Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology by the local laboratories and by IHMA.
- A total of 3,997 isolates of *S. pneumoniae* were collected between 2010-2015 and compared to 2,173 isolates collected between 2004-2009 [1].
- Isolates from 2010-2015 were from sterile body sites including blood (n = 2,308; 57.7%), body fluids (n = 214; 5.4%), sterile respiratory sites, including lungs, bronchia, and sinuses (n = 1,193; 29.8%), and other sterile body sites including central nervous system, cardiovascular system, lymph nodes, reproductive tissues, muscle, and bone (n = 282; 7.1%).
- Isolates from 2004-2015 were from Europe (48.6%), North America (37.2%), Latin America (5.2%), the Middle East (3.0%), Asia (2.3%), Africa (2.0%), and the South Pacific (1.6%) [Table 1].
- Serotypes were determined by PCR
 - Isolates non-typeable by PCR were serotyped by the Quellung reaction.
 - Minimum inhibitory concentrations (MIC) were determined by broth microdilution and interpreted using CLSI guidelines [2].
 - Penicillin parenteral meningitis breakpoints were applied to isolates from central nervous system sources, including cerebral spinal fluid (≤0.06 mg/L, susceptible; ≥0.12 mg/L, resistant).
 - Non-meningitis breakpoints (≤2 mg/L, susceptible; 4 mg/L, intermediate; ≥8 mg/L, resistant) were used for isolates from all other infection sources.

Table 1. Geographic distribution of serotyped isolates (n=6,170)

Region	Country	No. of isolates	Time period (yr)		
			2004-2009 (n)	2010-2012 (n)	2013-2015 (n)
Total		6170	2173	2064	1933
Europe					
	Austria	13	2	11	--
	Belgium	182	43	57	82
	Bulgaria	23	--	23	--
	Croatia	23	6	13	4
	Czech Republic	17	9	4	4
	Denmark	64	27	22	15
	Finland	24	10	6	8
	France	536	56	256	224
	Germany	352	56	145	151
	Greece	23	15	7	1
	Hungary	24	8	10	6
	Ireland	95	3	57	35
	Italy	486	95	170	221
	Latvia	18	8	10	--
	Lithuania	15	4	11	--
	Netherlands	30	--	9	21
	Poland	30	6	11	13
	Portugal	145	4	62	79
	Romania	5	--	5	--
	Slovak Republic	1	--	1	--
	Slovenia	6	4	2	--
	Spain	709	67	338	304
	Sweden	43	14	25	4
	Switzerland	79	13	31	35
	The Netherlands	8	8	--	--
	United Kingdom	50	10	18	22
North America					
	Canada	2293	1279	474	540
	United States	302	65	104	133
	United States	1991	1214	370	407
Latin America					
	Argentina	322	144	81	97
	Brazil	94	58	35	1
	Chile	25	18	1	6
	Colombia	42	17	--	25
	Honduras	37	14	15	8
	Jamaica	1	1	--	--
	Mexico	5	5	--	--
	Panama	59	18	17	24
	Venezuela	45	4	11	30
	Venezuela	14	9	2	3
Middle East					
	Israel	188	84	87	17
	Jordan	126	72	54	--
	Kuwait	17	--	9	8
	Oman	9	--	5	4
	Saudi Arabia	4	--	--	--
	Saudi Arabia	32	8	19	5
Asia					
	China	142	73	48	21
	India	16	9	7	--
	Malaysia	6	6	--	--
	Pakistan	21	7	12	2
	Singapore	10	5	--	5
	South Korea	41	24	8	9
	Taiwan	27	15	12	--
	Taiwan	12	7	--	5
	Thailand	9	--	9	--
Africa					
	Mauritius	125	42	56	27
	Morocco	4	4	--	--
	South Africa	60	--	40	20
	Tunisia	49	38	9	2
	Tunisia	12	--	7	5
South Pacific					
	Australia	99	83	14	2
	Philippines	77	63	14	--
	Philippines	22	20	--	2

Results

- Worldwide, in the most recent (2013-2015) time period, serotypes 19A (10.7%), 35B (8.3%), 11A (7.1%), 15B (6.0%), 24F (6.0%), 15A (4.8%), and 19F (4.8%) were the most common in children under 2 years of age. In adults ≥65 years of age, serotypes 3 (13.7%), 19A (6.9%), 22F (6.5%), 11A (6.2%) and 35B (4.5%) were the most common.
- Overall, the proportion of disease caused by PCV13 serotypes, which includes the 10 serotypes found in PCV10, declined globally when comparing the 2004-2009 time period to the 2010-2012 and 2013-2015 time periods [Figure 1 and Table 2].
- The proportion of disease caused by serotypes unique to PPV23 as well as those serotypes not included in any pneumococcal vaccine increased in all age groups during the 2010-2015 time period [Table 2]. The reason for these changes cannot be deduced from the limited available data for this study.
- In the 2013-2015 time period, serotypes 33F, 15A, 19A, and 9V exhibited the highest levels of erythromycin resistance (MICs ≥1 mg/L), while 19A, 14, 10B, and 9V demonstrated the highest rates of penicillin-intermediate (MIC 4 mg/L) isolates [Table 3]. Forty-two (2.2%) and twelve (0.6%) isolates of varying serotypes were penicillin-resistant (MIC ≥0.12 mg/L, meningitis; MIC ≥8 mg/L, non-meningitis) and levofloxacin-resistant (MIC ≥8 mg/L), respectively.

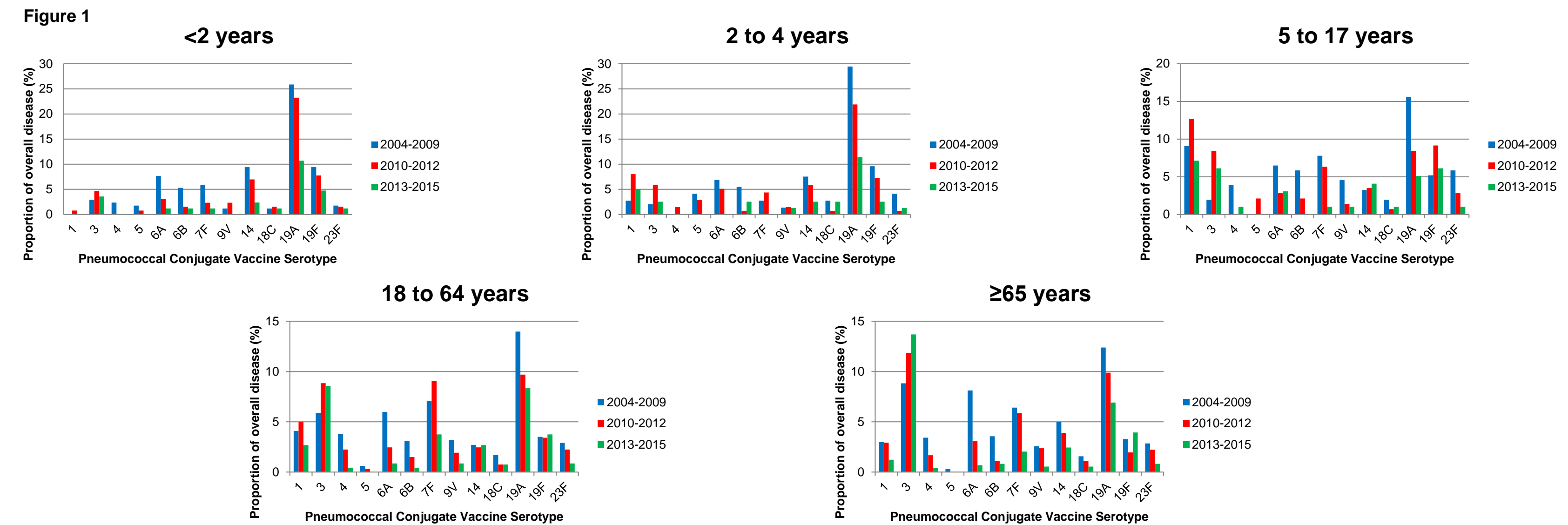


Table 2. Percentage of isolates by vaccine, time period and age group

	<2 years		2 to 4 years		5 to 17 years		18 to 64 years		≥65 years	
	2004-2009 (n=170)	2010-2015 (n=213)	2004-2009 (n=146)	2010-2015 (n=216)	2004-2009 (n=154)	2010-2015 (n=240)	2004-2009 (n=1001)	2010-2015 (n=1873)	2004-2009 (n=702)	2010-2015 (n=1455)
PCV7 Serotypes	30.6% (n=52)	17.4% (n=37)	30.8% (n=45)	16.2% (n=35)	30.5% (n=47)	17.5% (n=42)	20.9% (n=209)	12.1% (n=227)	22.2% (n=156)	11.9% (n=173)
PCV10 Serotypes	38.2% (n=65)	20.2% (n=43)	40.4% (n=59)	27.8% (n=60)	47.4% (n=73)	33.3% (n=80)	32.7% (n=327)	22.5% (n=422)	31.9% (n=224)	17.9% (n=260)
PCV13 Serotypes	74.7% (n=127)	45.1% (n=96)	78.8% (n=115)	53.7% (n=116)	71.4% (n=110)	50.8% (n=122)	58.5% (n=586)	41.9% (n=785)	61.3% (n=430)	40.9% (n=595)
PPV23 unique Serotypes	15.9% (n=27)	21.6% (n=46)	11.0% (n=16)	17.6% (n=38)	14.9% (n=23)	16.3% (n=39)	24.8% (n=248)	28.5% (n=533)	19.9% (n=140)	27.8% (n=404)
Not in any vaccine	9.4% (n=16)	33.3% (n=71)	10.3% (n=15)	28.7% (n=62)	13.6% (n=21)	32.9% (n=79)	16.7% (n=167)	29.6% (n=555)	18.8% (n=132)	31.3% (n=456)

Serotypes contained in each pneumococcal vaccine: PCV7 (4, 6B, 9V, 14, 18C, 19F, 23F); PCV10 (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F); PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F); PPV23 unique (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F). Not in any vaccine: excludes serotypes contained in PCV7, PCV10, PCV13, and PPV23.

Table 3. Serotypes with the highest percentages of erythromycin-resistant (A) and penicillin-intermediate (B) isolates observed in the 2013-2015 time period, all ages.

A	Serotype	n	ERY-R (n (%))
	33F	33	27 (81.8%)
	15A	72	54 (75.0%)
	19A	152	108 (71.1%)
	9V	14	9 (64.3%)
	11D	5	3 (60.0%)
	6A	17	10 (58.8%)
	19F	76	44 (57.9%)
	33A	14	8 (57.1%)

B	Serotype	n	PEN-I (n (%))
	19A	152	30 (19.7%)
	14	51	10 (19.6%)
	10B	6	1 (16.7%)
	9V	14	2 (14.3%)
	6A	17	1 (5.9%)
	23F	17	1 (5.9%)
	17F	17	1 (5.9%)
	19F	76	4 (5.3%)

n, number of isolates; ERY-R, erythromycin-resistant (MIC ≥1 mg/L); PEN-I, penicillin-intermediate (MIC =4 mg/L; does not include isolates collected from infections of the central nervous system).

Strengths and Limitations

- This study describes the serotypes found in a large, global collection of *S. pneumoniae* clinical isolates collected over an eleven year period spanning the widespread introduction of PCV10 and PCV13 vaccination programs in 2010.
- This dataset, though extensive, is a convenience sample and cannot be considered representative.
- The vaccine uptake for all vaccines examined in this study is not known.
- This study only analyses the role of vaccine use in driving pneumococcal serotype evolution and does not assess the role played by antibiotic use, which is another major selective pressure on serotype evolution.

Conclusions

- This analysis of an existing isolate database found serotypes 3 (9.9%), 19A (7.9%), 11A (5.5%), 22F (5.2%), 35B (5.1%) and 8 (4.4%) to be the most common global serotypes in the most recent sampling period (2013-2015).
- These data add to the body of literature that demonstrates that the use of PCVs globally has resulted in significant reduction in invasive pneumococcal disease caused by the serotypes contained in the vaccines.
- Direct vaccination of adults with PCV13 may be useful in reducing disease caused by serotypes included in this vaccine, such as 3 and 19A, in adults.
- Susceptibility of *S. pneumoniae* to antimicrobial agents commonly used as part of empiric therapy further documents the value of vaccination programs and the need for ongoing monitoring of the seroepidemiology of this important pathogen.

References

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- Clinical and Laboratory Standards Institute. 2017. M100-S27. Performance standards for antimicrobial susceptibility testing, 27th informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.