The Contribution of Specific Pneumococcal Serogroups to Different Disease Manifestations: Implications for Conjugate Vaccine Formulation and Use, Part II

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To assess whether certain serogroups of *Streptococcus pneumoniae* are preferentially associated with specific disease manifestations, we analyzed all recent pneumococcal disease studies and assessed the relative frequency of isolation of each serogroup by clinical site (as a proxy for different disease states). In all age groups, serogroups 1 and 14 were more often isolated from blood, and serogroups 6, 10, and 23 were more often isolated from cerebrospinal fluid (CSF); in young children, serogroups 3, 19, and 23 were more often isolated from middle ear fluid (MEF). Serogroups represented in conjugate vaccines were isolated slightly less frequently from CSF than from blood or MEF. Nonetheless, serogroups in the 9-valent conjugate vaccine formulation still comprised ~75% of pneumococcal isolates from the CSF of young children in Europe and in the United States and Canada. These analyses indicate that pneumococcal conjugate vaccines could potentially prevent a substantial proportion of episodes of bacteremic disease, pneumonia, meningitis, and otitis media, especially in young children.

Pneumococci are responsible for a wide variety of disease manifestations. In the United States alone, it is estimated that pneumococci annually account for 3000 cases of meningitis, 50,000 cases of bacteremia, 500,000 cases of pneumonia, and 7 million cases of otitis media [1]. Globally, ~1.2 million deaths due to pneumococcal pneumonia and meningitis are believed to occur among young children every year, mostly in developing countries [2]. Although the focus has been on pneumonia, pneumococcal meningitis is of exceptional severity [3, 4].

More than 90 pneumococcal serotypes, immunologically distinguishable by their polysaccharide capsules, can potentially cause disease. There are at least 40 serogroups, some comprising multiple serotypes that are immunologically cross-reactive. Current pneumococcal vaccine formulations are combination vaccines containing a mixture of the capsular polysaccharides from the more common serotypes and are effective against invasive disease in older children and adults [5].

The new protein-saccharide conjugate vaccines offer great promise in eliciting protective immune responses to these saccharides, even in infants. They raise the prospect that 1 or a limited number of vaccine formulations could conceivably prevent the major manifestations of pneumococcal disease in all age groups in every region.

To address this possibility, one must first ascertain how many and which serotypes cause the majority of cases of pneumococcal disease. The accompanying article (see preceding article in this issue), which analyzed the large number of epidemiological studies published in the past few years, presented an initial determination of the potential effectiveness of various conjugate vaccine formulations against invasive pneumococcal disease (IPD) in different age groups, by geographic region [6]. However, there are additional complexities to be taken into account when one is evaluating the potential of the vaccine formulations to prevent each major disease manifestation, both invasive and noninvasive [7].

For example, on the basis of limited data, various investigators [8–10] have proposed that some serotypes have a propensity to invade one clinical site rather than another and may therefore be disproportionately responsible for certain disease manifestations. In addition, demonstration of vaccine efficacy against 1 disease manifestation (e.g., bacteremia without a focus) may not necessarily predict efficacy against another (e.g., otitis media) [7].

In light of the above considerations, the present study further analyzes the recent studies that present serogroup and/or serotype information separately for different clinical sites of isolation (as surrogates for different invasive and noninvasive disease states), to enable better understanding of the disease-causing tendencies of the most common serogroups. The results of these analyses are then compared with the serogroup composition of various conjugate vaccine formulations to assess

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the potential of each to prevent each major manifestation of pneumococcal disease.

Methods

Sources. The MEDLINE data base and Current Contents were used to identify all articles published in the scientific and medical literature that described the serogroups and/or serotypes of pneumococcal isolates from normally sterile sources that had been collected since 1987 from patients with clinical disease. In addition, we obtained copies of reports of some national reference laboratories, including studies that provided sufficient demographic information to categorize isolates as being exclusively or predominantly from very young children or from older children/adults [6] (table 1). These comprised the invasive-disease studies described in the previous study [6], augmented by studies specifically containing information about middle-ear-fluid (MEF) isolates.

Most serogroup data were originally identified by isolate source—in the vast majority of cases, this was blood, CSF, and/or MEF—rather than by disease manifestation, and we analyzed the data accordingly. Generally, isolates categorized as being from CSF were clearly identified, but in a few studies in which both blood and CSF were cultured, some isolates were identified only as being from "meningitis patients." These "meningitis" isolates were included in the CSF category, since in other studies at least 90% of the meningitis cases were diagnosed on the basis of recovery of pneumococcal isolates from CSF.

Because there were relatively few recent studies involving MEF, we included all MEF data sets containing data collected since 1975. Inclusion criteria, age, and geographic groupings were otherwise as described elsewhere [6]. In addition, we did a separate comparison of serogroup distribution among CSF and MEF isolates versus distribution among isolates from blood or pleural fluid from patients with pneumonia. We did not include any nasopharyngeal isolate data in this survey.

Statistical methods. In most studies the selection of cases was not based on a specified sampling plan; thus, it is not realistic to think of study results as representative of conditions in a well-defined study population. In addition, studies differed in certain methodological aspects. For these reasons, statistical tests of between-study differences (e.g., formal tests of differences in coverage of a specific formulation between continents or other geographic regions) were avoided. For certain comparisons that could be made on the basis of data from within the same study, formal statistical tests were performed as follows.

Comparison of the coverage of specific vaccine formulations between young children and older children/adults, controlled for source of isolate (test 1). Studies were identified in which isolates were obtained from a common source (either CSF or blood) for both age groups; the source-specific proportions of cases caused by serogroups corresponding to the 7-, 9-, 11-, and 23-valent vaccines were calculated by age group, and study-specific CIs for the coverages of these formulations were computed by use of the exact binomial method. Source- and study-specific tests for differences in coverage in young children versus older children/adults were conducted by use of Fisher's exact test. As a control on multiple testing, and to combine data across studies, tests were aggregated across comparisons by means of the Mantel-Haenszel method.

Comparison of the cumulative coverage curves for young children and older children/adults, controlled for source of isolate (test 2). We also compared source-specific cumulative coverage curves for young children and older children/adults by using matched studies in which isolates were obtained from a common source. For each study in which isolates were obtained from either CSF or blood from both age groups, source-specific cumulative coverage curves were computed, and the ordinate C_{50}, at which these curves achieved 50% coverage, was determined for both age groups (generally, 50% coverage was not achieved exactly for any integer value of the ordinate, in which case C_{50} was determined by interpolation). Differences in C_{50} for young children versus older children/adults were compared across all matched comparisons by means of the Wilcoxon signed-rank test.

Comparison of the coverage of specific vaccine formulations between isolate sources, controlled for subjects' ages (test 3). The coverages of the 7-, 9-, and 11-valent vaccines were also compared among various sources of isolates (MEF, CSF, blood, or pneumonia isolates, as defined above), after age group (younger children vs. older children/adults) and study were controlled for. For example, to compare the coverage of a particular vaccine formulation in MEF and CSF among young children, all studies having data relevant to this comparison were identified, and study-specific CIs for coverage in MEF and CSF were computed as in test 1 above. Study-specific comparisons in coverage were tested by use of Fisher's exact test, and aggregated comparisons were tested by use of the Mantel-Haenszel statistic. Similarly, comparisons of cumulative coverage curves between pairs of isolate sources were tested by methods analogous to those of test 2 above, by use of matched pairs defined by study and age group.

Screening of individual serogroups. To help interpret differences found in test 3, a screening study was undertaken in which selected serogroups were compared across isolate sources with respect to the proportion of disease attributable to each serogroup. Serogroups were included in this screening if they contributed at least 2% of all disease, averaged across all studies. The methods used in the screening study were identical to those described in test 3, applied at the individual serogroup level.

To control for multiple testing, the screening of differences between each pair of isolate sources was contingent on the statistical significance of a preliminary omnibus test, in which cases were categorized into 1 of 8 mutually exclusive types: serogroup 4, 6, 9, 14, 18, 19, 23, or "other." For each study comparing the selected pair of isolate sources in a given age group, a 2×8 contingency table was generated, whose rows represented the isolate sources being compared and whose columns represented the serogroup categories listed above. These tables were aggregated over age-matched studies with use of the Cochran–Mantel-Haenszel statistic.

Vaccine formulations. The 7-valent vaccine formulation (7-V) of 2 major manufacturers include conjugates derived from polysaccharides or oligosaccharides from types 4, 6B, 9V, 14, 18C, 19F, and 23F. The 9-valent vaccine formulation (9-V) is 7-V plus serotypes 1 and 5. The 11-valent vaccine formulation (11-V) is 9-V plus serotypes 3 and 7F.

Table 1. Pneumococcal serotypes isolated from blood, expressed as a percentage of all serotypes and ranked in decreasing importance for each region or country.

Population and site of study	Ref(s)	Study years	No. of subjects	Age, y	1st	2d	3d
Young children							
United States and Canada					14	6 (A/B)	19 (A/F)
Alabama	[11]	1985–89	265	94% <6	25.7	18.9	15.8
United States	[12]	1978–94	3169	<6	28.8	16.2 (3.4/12.8)	14.4 (3.5/10.9)
Colorado	[13]	1989–94	65	<15	38.5	12.3	4.6
Canada	[14]	1984–86	44	<18	38.6	4.5	13.6
Asia					1	19 (A/F)	5
Bangladesh	PC[a]	1993–94	148	<2	14.2	11.4	5.4
Bangladesh	[15]	1992–95	71	<5	5.6		
China	[16]	1982–85	67	31% >14	29.9	3	16.4
India	[17]	1988–92	33	<13	33.3	0	9.1
Pakistan	[18]	1986–89	87	<5	1.1	44.8 (12.6/32.2)	2.3
Israel	[19]	1987–92	119	<14	10.1	12.6 (7.6/5)	13.4
Israel	[20]	1988–90	213	<13	20	7	15
Africa					6	14	1
S. Africa	[21]	1993–95	98	<13	28.5	15.3	12.2
Europe					14	19 (F)	6 (A/B)
Finland	[22]	1985–89	248	<16	22.2	16.5	19
Netherlands	[23][b]	1996	29	<5	17.2	20.7	10.3
Germany	[24]	1992–96	80	<14	12.5	8.8 (8.8)	13.8 (8.8/5)
Spain	[25][c]	1979–94	263	<14	14.9	17.5	13.3
France	[26]	1996	103	<15	19.4	13.6	14.6
Latin America					6 (A/B)	5	19 (F)
Colombia	[27]	1994–98	36	<5	25 (3/22)	11.1	11 (11)
Oceania					14	19	6
New Zealand	[28, 29][d]	1989–92	100	<14	25	18	15
					14	6 (B)	19 (A/F)
Australia	PC[c]	1994–96	161	<2	46.6	13 (13)	9.9 (9.3/0.6)
Older children and adults							
United States and Canada					4	9	14
Colorado	[13]	1989–94	191	>14; 90% >30	13.1	12.5	10.5
					4	14	9 (N/V)
Ohio	[30]	1991–92	258	>17	12.8	12	10.4 (2.3/8.1)
Asia					1	19 (A/F)	3
India	[17]	1988–92	37	>12	37.8	5.4	0
Israel	[31]	1993	398	>15; 69% >55	14.1	8.5	10.6
Israel	[20]	1987–92	129	>13; mdn, 64	10.1	10.1 (6.2/3.9)	4.7
Africa					1	7	5
Kenya	[32]	1991–92	75	"Adults"	20	16	10.7
					1	14	19
S. Africa	[21]	1993–95	359	>13	33.4	12	11.4
Europe					1	14	9 (N/V)
Netherlands	[23][b]	1996	697	>4	14.6	9.6	8.3
Spain	[25][c]	1979–94	1440	>14	4.2	8.8	7.8
Spain	[33]	1979–90	386	"Adults"	8.5	2.1	9.3
Switzerland	[34]	1992–94	92	91% >10; 52% >50	4.3	9.8	9.8
Sweden	[35]	1981–92	50	>14	0	14	14 (4/10)
Finland	[36]	1983–92	862	>16		8.7	11.5
Denmark	[37]	1989–94	4062	89% >14	13.7	8.6	9 (2.5/6.5)
France	[26]	1996	787	>14	4.4	17	9.8
Oceania					14	4	9 (N/V)
Australia	PC[e]	1994–96	542	>2	21.2	12.2	11.3 (3.7/7.6)

NOTE. Mdn, median; PC, personal communication; ref, reference.

[a] P. Vaughan.

[b] A. van der Ende and J. Dankert.

[c] A. Fenoli and J. Casal.

[d] D. Martin.

[e] G. Hogg and J. Strachan.

% of all serotypes isolated from blood								
4th	5th	6th	7th	8th	9th	10th	11th	12th
18 (C)	4	9 (V)	23 (F)	12	7	1	15	3
8.7	4.9	9	4.9	1.9	1.1	0.8	1.1	0.4
8.1 (8.1)	7.1	6.4 (6.4)	6.6 (6.6)					0.8
10.8	4.6	7.7	4.6	3.1	1.5	1.5	0	1.5
13.6	11.4	4.5	4.5		2.3		2.3	0
14	6 (A/B)	9 (A/N/V)	18 (A/C)	7 (F)	23 (F)	31	15 (B/C)	16 (F)
4.1	8.7	9.5	2.7	0.7	2.7		1.4	
9.9	4.2 (4.2/0)			16.9 (16.9)	7 (7)		11.3 (11.3/0)	4.2 (4.2)
9	7.5	1.5	0	3	3	0	1.5	0
0	12.1	0	0	6.1	0	0	15.2	0
0	5.7 (4.6/1.1)	11.4 (1.1/0/10.3)	1.1	0	0	14.9	4.6 (0/4.6)	13.8
8.4	3.3 (2.5/0.8)	7.5 (0/2.5/5)	10.1	5.9 (5.9)	5 (5)		1.7	0.8 (0.8)
15	11 (4/7)		7	4 (4)	5	0		
19	23	15	3	4	18	5	11	17
12.2	11.2	4.1	3.8	3.8	3.1	1.9	1	1
23 (F)	18 (C)	9 (V)	1	4	24	5	7 (F)	3
7.3	10.1	6		4.8			6.5	
3.4	13.8	3.4	3.4	0			6.9	3.4
6.3 (6.3)	10 (10)	11.3 (11.3)		10			2.5 (2.5)	6.3
12.2	7.2	4.6	4.9			6.5	3.4	3.4
11.7	8.7	6.8	8.7	2.9	4.8	0	1.9	0
14	18 (C)	1	23 (F)					
8.3	6 (6)	5.6	5.5 (5.5)					
23	1	7	18	4	9	12	33	10
8	5	5	4	3	3	3	3	2
23 (F)	9 (V)	18 (C)	4	15 (B)	3	7 (F/A)	10	
6.2 (6.2)	5.6 (5.6)	5 (5)	4.3	1.2 (1.2)	0.6	0.6 (0.6/0.6)	0.6	
12	6	3	1	19	20	18	22	7
8.4	6.3	6.2	4.7	4.7	4.7	4.2	3.2	3.2
23 (F)	19 (A/C/F)	6 (A/B)	1	3	12 (F)	22 (A/F)	11 (A)	8
9.7 (9.7)	9.4 (3.9/1.2/4.3)	8.9 (2.7/6.2)	6.2	5	4.3 (4.3)	3.5 (0.4/3.1)	3.1 (3.1)	2.3
5	14	23 (F)	7 (F)	6 (A/B)	12 (A/F)	9 (N/V)	4	10 (A)
10.8	0	5.4	0	8.1	0	0	0	0
6.5	7.5	7	7.5	3	5.5	4.5	2.5	4.5
8.5	8.5	3.9 (3.9)	2.3 (2.3)	12.4 (3.1/9.3)	5.4 (3.1/2.3)	2.4 (0.8/1.6)	7	0.8 (0.8)
3	12	10	18	19	23	2	8	11
8	6.7	4	4	4	4	2.7	2.7	2.7
6	3	15	4	18	9	7	8	5
9.5	6.7	3.9	3.6	2.8	2.8	2.5	2.5	1.7
4	3	7 (A/C/F)	6 (A/B)	19 (A/F)	23 (A/B/F)	8	12 (A/F)	5
8.6	5	8.9	5.6	5	5	4.4		
7.1	13.3		4.5	6.8	6.2	7.5		4.9
7.5	13	4.4	5.7	4.7	4.9	6	2.6	8
5.4	5.4	14.1	19.6	9.8	5.4			
8	10	10 (0/0/10)	2 (0/2)	10 (6/4)	8 (0/0/8)	4	0	0
10.6	13	10	6.7	8	5.8	5.8	2.9	
8.8	5.4	7.3 (0.1/0.1/7.1)	7.6 (3.5/4.1)	5.4 (2.4/3)	4.1 (0.4/0.1/3.6)	3.8	4.9 (0.2/4.7)	3
6.6	7.2	4.1	6.4	8.6	7.8	4.4	1	0.9
19 (A/F)	6 (A/B)	23 (F)	3	18 (C)	22 (F)	1	7 (F)	11 (A)
10.2 (8.5/1.7)	9.6 (2.8/6.8)	7.9 (7.9)	5.2	4.4 (4.4)	3.9 (3.9)	2.4	1.8 (1.8)	1.3 (1.3)

Table 2. Pneumococcal serotypes isolated from CSF, expressed as a percentage of all serotypes and ranked in decreasing importance in each region or country.

Population and site of study	Ref(s)	Study years	No. of subjects	Age (y)	1st	2d	3d
Young children							
United States and Canada					6 (B/A)	14	19 (A/F)
Alabama	[11]	1985–89	38	94% <6	22.2	7.9	13.9
United States	[12]	1978–94	401	<6	25.7 (21.2/4.5)	21.7	11.9 (3.2/8.7)
Massachusetts	[38]	1990–91	31	<6	32.3	9.7	
Asia					2	5	7 (F)
China	[16]	1982–85	169	13.6% >13	19.5	16	2.4
Bangladesh	[15]	1992–95	94	<5			22.3 (22.3)
India	[17]	1988–92	82	<13	0	6.1	8.5
Africa					1	14	19 (F/A)
Egypt	[39]	1977–78; 1992	59	<6	30.5	5.1	3.4
Ethiopia	[40]	1993–95	46	91% <5; 77% <1	8.7	23.9	21.7 (21.7/0)
Rwanda	[41]	1984–90	76	<10	26.3	13.2	5.3
Europe					6 (B/A)	14	18 (C)
Finland	[22]	1985–89	46	<16	15.2	6.5	6.5
France	[26]	1996	41	<15	24.4	14.6	9.8
Germany	[24]	1992–96	41	<14	14.7 (4.9/9.8)	12.2	14.6 (14.6)
Spain	[25][a]	1979–94	59	<14	30.5	13.6	15.3
England	[50]	1990–93	28	<5	25 (21.4/3.6)	28.6	10.7 (10.7)
Netherlands	[23][b]	1996	63	<5	17.5	15.9	9.5
Netherlands	[43]	1974–94	55	<18	9.1 (0/9.1)	16.4	10.9
Latin America					6 (B/A)	14	5
Brazil	[44]	1977–92	645	<2	18.1 (11/7.1)	11	7.3
Brazil	[45]	1993–96	158	<6		15.2	
Colombia	[27]	1994–98	132	<5	19.6 (9.8/9.8)	21.9	9.1
Uruguay	[46]	1994–96	42	<5	14.3	19	23.8
Chile	[47]	1994–96	106	<5	8.5 (5.7/2.8)	8.5	17
Oceania					6	14	5
Papua New Guinea	[48]	1980–84	67	<5	9	3	16.4
Australia	PC[c]	1994–96	22	<2	22.7	45.4	0
New Zealand	[28, 29][d]	1989–92	29	<14	20.7	17.2	0
Older children and adults							
Asia					1	3	7
India	[17]	1988–92	33	>12	24.2	18.2	15.2
Africa					1	10 (A/F)	6 (A)
Egypt	[39]	1977–78; 1992	72	>5; 33% 6–12; 10% >36	33.3	8.4 (2.8/5.6)	6.9 (6.9)
					1	25	18
Rwanda	[41]	1984–90	20	>9	15	15	10
Europe					6 (B/A)	19 (F/A)	9 (V/N/A)
Netherlands	[23][b]	1996	173	>4	8.7	10.4	11.6
Spain	[25][a]	1979–94	169	>13	7.1	11.2	7.7
Spain	[23]	1979–90	84		10.7	3.6	11.9
Switzerland	[34]	1992–94	33	9% <10; 5% <2; 52% >50	3	15.2	3
Belgium	[49]	1980–93	462	75% >5; 53% >50	12.6	11.3	7.6
Sweden	[35]	1981–92	28	>14	10.8 (3.6/7.2)	10.7 (10.7/0)	7.2 (7.2/0/0)
Finland	[36]	1983–92	97	>16	3.1	7.2	7.2
Denmark	[37]	1989–94	558	10% <14; 89% >14	13.7 (8.1/5.6)	5.2 (4.5/0.7)	6.5 (4.7/1.8/0)
France	[26]	1996	73	>15	5.5	6.9	15.1
England	[50]	1990–93	37	>5	16.2 (10.8/5.4)	2.7 (0/2.7)	8.1 (5.4/0/2.7)
Latin America					1	6 (B/A)	3
Brazil	[44]	1977–92	574	>2	17.4	8.4 (3.5/4.9)	8
Oceania					19 (A/F)	3	6
Australia	PC[c]	1994–96	30	⩾2	20 (16.7/3.3)	16.7	13.3

NOTE. PC, personal communication; ref, reference.

[a] A. Fenoll and J. Casal.

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% of all serotypes isolated from CSF								
4th	5th	6th	7th	8th	9th	10th	11th	12th
18 (C)	23 (F)	4	9 (V)	8	10	12	34	3
2.6 9.2 (9.2) 25.8	13.9 9 (9)	13.9 3	10.1 2.7 (2.7)	2.6	2.6	2.6	2.6	0 1.5
12 (F)	6	27	1	14	23	15 (B)	3	19
3.6 16 (16) 3.7	8.3 3.7	7.1 8.5	4.7 7.4 13.4	5.3 10.6 0	5.3 6.1	2.4 9.6 (9.6) 0	2.4 8.5	1.8 8.5
12 (A)	6 (B/A)	5	9 (L/N)	20	7 (F/A)	18 (A/F)	4	29
6.8 (6.8)	8.5 (1.7/6.8) 2.2 7.9	1.7 6.5 9.2	8.5 (8.5/0) 2.2 (0/2.2)	3.4 8.7	5.1 (1.7/3.4) 4.3	3.4 (1.7/1.7) 6.5 3.9	3.4	3.4
19 (A/F)	9 (V/A)	23 (F)	7 (F)	4	15 (B)	1	3	8
15.2 4.9 7.3 (0/7.3) 10.2 10.7 (10.7/0) 12.7 18.2	8.7 9.8 7.3 (7.3/0) 10.7 (3.6/7.1) 7.9	4.3 17.1 4.9 (4.9) 9.5 1.8	10.9 2.4 12.2 (12.2) 3.4 6.3 5.5 (5.5)	8.7 4.9 4.9 5.1 3.2 7.3	 4.9 1.8 (1.8)	 0 1.7 3.6 4.8 1.8	 2.4 4.9 1.7 0 5.5	 2.4 1.7 0 5.5
18 (C/F/A)	23 (F/B)	1	19 (A/F)	9 (N/V)	7 (F)	4	10 (A)	22 (F)
8 (6.8/0/1.2) 5 (5/0/0) 6.1 (6.1/0/0) 11.9 7.6 (5.7/1.9/0)	6.9 (5.7/1.2) 12.1 (12.1/0) 2.4 (0/2.4) 3.8 (3.8/0)	8.4 7.6 2.3 2.4 5.7	7.6 (2.2/5.4) 6.3 (0/6.3) 6.8 (0/6.8) 4.8 (0/4.8) 4.7 (2.8/1.9)	4.5 (2.2/2.3) 0 0	2.2 (2.2) 7.1 3.8 (3.8)	2.3 2.8	2 (2) 	 1.9 (1.9)
7 (F)	2	46	23 (F)	8	18 (C)	12	19 (A)	45
13.4 4.5 (4.5) 0	9 0 0	9 0 0	6 9.1 (9.1) 0	4.5 0 10.3	1.5 9.1 (9.1) 6.9	6 0 3.4	0 9.1 (9.1) 10.3	6 0 0
5	13	6	15	19				
12.1	12.1	6.1	6.1	3				
9 (L)	19 (A)	29	34	4	11 (A)	12 (A)	20	38
5.6 (5.6)	5.6 (5.6)	5.6	4.2	2.8	2.8 (2.8)	2.8 (2.8)	2.8	2.8
19								
5								
23 (F/A/B)	3	14	7 (F/B)	18 (C)	4	12 (F)	8	24 (F)
6.4 8.9 10.7 9.1 8.4 17.9 (17.9/0/0) 10.3 4.7 (3.9/0.7/0.1) 12.3 5.4 (5.4/0/0)	11.6 14.8 9.5 9.1 5.2 3.6 8.2 5.7 5.5 10.8	4 8.9 1.2 12.1 8.7 10.7 5.8 6.6 11 8.1	6.9 4.8 0 5.8 7.2 (7.2/0) 5.2 9.3 (9.2/0.1) 2.7 2.7 (2.7/0)	4.6 5.3 4.8 18.2 7.8 3.6 (3.6) 5.6 (5.6) 5.5 2.7 (2.7)	6.4 4.8 3.7 8.2 7 1.4	 5.3 7.1 3.2 3.6 (3.6) 3.1 5 (5) 1.4	4.6 5.3 8.3 4.1 3.6 5.2 3.1 0 8.1	 0 2.4 0 4.7 (4.7) 2.7
18 (A/C)	12 (F)	23 (F/B)	19 (F/A)	9 (V/N)	7 (F)	8	4	5
5.7 (1.2/4.5)	5.2 (5.2)	4.5 (3/1.2)	4.4 (3/1.4)	3.9 (1.6/2.3)	3.7 (3.7)	3.7	3.1	3.1
9 (N)	11 (A)	14	18 (C)	1	4	7 (F)	23 (F)	33 (F)
6.7 (6.7)	6.7 (6.7)	6.7	6.7 (6.7)	3.3	3.3	3.3 (3.3)	3.3 (3.3)	3.3 (3.3)

Table 3. Pneumococcal serotypes isolated from middle ear fluid (MEF) and from the blood and pleural fluid (PF) of pneumonia patients, expressed as percentage of all serotypes and ranked in decreasing order of importance within each region.

Population and site of study	Ref(s)	Study years	No. of subjects	Age (y)	1st	2d	3d
Young children, MEF isolates							
United States and Canada					19 (F/A)	6 (B/A)	23 (F)
United States	[51]	1970; 1977–79	1837	<12	23	12	12.5
United States	[12]	1978–94	314	<6	22 (15.3/6.7)	14 (10.2/3.8)	13.1 (13.1)
Alabama	[11]	1985–89	228	94% <6	33.2	14	14
Kentucky	[52]	1992–94	153	2 mo–15 y	22.2 (16.3/5.9)	17 (13.1/3.9)	8.5 (8.5)
Europe					19 (F)	6 (B/A)	14
Spain	[25][a]	1979–94	419	<14	22	17.7	13.1
Belgium	[49]	1980–93	691	86% <10	25.3	14	10.1
France	[26]	1996	566	4.2% >15	16.1	17.3	24
Finland	[53]	1977–79	212	<7	23 (18.4)	21 (12.6/8.4)	
Finland	[54]	1979–81	295	95% <9 mo	25.4 (17.1)	18.6 (8.6/10)	8.2
Oceania					19	3	14
Australia	[55]	1970–79	392	"Children"	24	16.1	11.7
Australia	[56]	1977–78	30	⩽8	20	13	23
Asia					19	6	5
China	[16]	1982–85	246	12.5% >13	14.6	13.4	10.2
Older children and adults, MEF isolates							
Europe					3	19	23
Spain	[25][a]	1979–94	84	>14	21.4	14.3	11.9
Young children, blood or PF isolates							
Latin America					14	1	5
Chile	[47]	1994–96	87	<5	25.3	11.5	14.9
Brazil	[45]	1993–96	189	<6	29.1	20.6	
Colombia	[27]	1994–98	133	<6	25.6	16.5	13.5
Uruguay	[46]	1994–96	104	<2	48.1	10.6	12.5
Uruguay	[57]	1987–89	48	<5	39.6	6.3	14.6
Oceania					14	19	6
Papua New Guinea	[48]	1978–88	88	<5	13.6	13.6	12.5
Asia					1	5	14
China	[16]	1982–85	67	31.4% >13	29.9	16.4	9
					7 (F)	15 (B)	12 (F)
Bangladesh	[15]	1992–95	71	<5	16.9 (16.9)	11.3 (11.3)	9.9 (9.9)
United States and Canada					14	9	19
Canada	[14]	1984–86	43	<18	25.6	18.6	14
Europe					1	14	23
France	[26]	1988–96	131	⩽13	22.1	14.5	13.7
Older children and adults, blood or PF isolates							
United States and Canada					4	3	9
Canada	[14]	1984–86	213	⩾18	16.4	12.7	9.4
Europe					14	3	1
England	[42]	1982–90	1896	6% ⩽5; 66% >60	15.2	13.9	11
					14	9	6
France	[26]	1996	238	>13	17.6	11.8	9.2

NOTE. PC, personal communication; ref, reference.

[a] A. Fenoll and J. Casal.

% of all isolates from MEF or from pneumonia patients								
4th	5th	6th	7th	8th	9th	10th	11th	12th
14	3	18 (C/B)	9 (V)	15 (B/C)	4	1	7 (F)	11 (A)
10.3	8.5	5.8	2.9	3.2	3.4	2.1	2.3	1.9
15	9.2	2.2 (2.2/0)	2.5 (2.5)		1.3			
10.9	6.1	2.2	4.4	1.3	0.9	1.8	0.4	3.1
7.8	13.1	3.3 (2.6/0.7)	11.1 (11.1)	1.3 (0.7/0.7)	1.3	3.3	0.7 (0.7)	0.7 (0.7)
23 (F)	3	9 (N)	18 (C)	7 (F)	1	15	11	5
11.5	8.8	5.3		1.7	3.8		2.1	1.7
9.8	10.6	4.1	3.6	4.1	4.2	2	2.3	2.3
19.8	4.6	9.5	1.9	0.9	0.2	1.2	1.4	0
13 (11.7)	11							
19.6 (19.6)	3.9	3.9 (3.6)	2.1 (2.1)	1.8 (1.1)	0	4.6	1.4	
23	6	18	9	1	4	11	5	7
7.4	7.4	4.8	4.8	4.3	3.3	2.5	2.3	2.3
7	0	10	3	0	7	3	3	3
23	3	14	1	15	33	18	7	12
8.9	8.1	7.7	4.5	4.1	3.7	2.4	2	2
14	6	9	35	8	11	17		
9.5	8.3	8.3	3.6	2.4	2.4	2.4		
6 (B/A)	3	19 (A/F)	9 (V)	7 (F/C)	23 (F/B)	15 (B/C)	21	18
13.7 (10.3/3.4)	4.6	10.3 (6.9/3.4)	2.3 (2.3)	4.5 (3.4/1.1)	1.1 (1.1/0)	2.2 (1.1/1.1)	2.3	0
		1.6 (0/1.6)						0.5
8.2 (4.5/3.7)		5.3 (0/5.3)			6.8 (6.8/0)			3
1.9	5.8	5.8 (5.8/0)	2.9 (2.9)	3.8 (3.8/0)	3.9 (2.9/1)			1
4.2 (4.2/0)	8.3	0	10.4 (4.2)	4.2 (4.2/0)	2.1 (0/2.1)	2.1 (0/2.1)	0	0
7	23	16	5	9	46	10	15	25
9.1	9.1	5.7	4.5	4.5	3.4	2.3	2.3	2.3
6	21	7	8	19	23	28	3	9
7.5	4.5	3	3	3	3	3	1.5	1.5
14	4	23 (F)	1	6 (A)	16 (F)			
9.9	7	7 (7)	5.6	4.2 (4.2)	4.2 (4.2)			
23	4	6	3	7	15	18	22	8
9.3	7	7	4.7	4.7	2.3	2.3	2.3	0
6	5	19	9					
13	6.9	6.9	6.1					
8	19	7	6	14	15	22	23	18
7.5	7.5	6.1	5.6	4.7	4.2	3.3	2.8	2.3
8	9	19	4	6	7	23	18	11
7.5	7.3	6.8	6.5	5.2	5.1	4.4	2.4	2.3
4	19	3	1	7	8	23	10	18
8	7.6	5.9	5.8	5.5	5.5	4.2	2.5	2.5

Results

In the preceding article [6], we analyzed >70 study reports that contained information about pneumococcal serogroup distribution among invasive isolates. Unfortunately, only a fraction of those study reports listed the serogroups by specific clinical site of isolation. Tables 1–3 show the 12 most commonly isolated serogroups among blood, CSF, and MEF isolates, respectively, for both young children and older children/adults, categorized by geographic region. For MEF isolates, almost all data are derived from young children in the United States and Canada and in Europe. Table 3 also contains the most commonly isolated serogroups for patients with pneumonia.

Table 4 provides weighted averages from tables 1–3 for those regions with ⩾3 studies in a given category. More detailed analyses are presented below, but for young children, serogroups 6 and 14 are each among the 5 most common isolates in every category, except CSF in Asia (where type 14 is 8th). For older children and adults, serogroups 3 and 14 are each consistently found among the 6 most common isolates. Outside the United States and Canada and Europe, serogroup 1 and/or 5 are among the 3 most frequently isolated serogroups in every category, and even in Europe these 2 serogroups together comprise at least 10% of the blood isolates from both age groups. Serogroups 1 and 5 also represent at least 20% of the isolates from young children with pneumonia in several Latin American countries, China, and France (table 3).

Number of serogroups responsible for a given percentage of disease, by clinical site and by age. We first wished to assess the relative diversity of serogroups from different clinical sites. Specifically, is a wider range of serogroups responsible for most blood isolates than for most CSF isolates? And is that range greater or less than the range for most MEF isolates? To assess this, for each study and isolate source we determined the percentage of contribution of the isolates (first, second, third, etc.) to the total and constructed cumulative curves.

Figure 1 *(left)* illustrates the weighted averages of such curves for European isolates. A consistent finding is that, within a single region and age group, the number of serogroups responsible for a given percentage of blood isolates does not appear to be substantially different from the number of serogroups responsible for the same percentage of CSF or MEF isolates. To further explore this, we evaluated those data sets from any region involving isolates from 2 different sources, and again we saw no statistically significant difference.

For example, there were 13 studies of young children and 10 of older children and adults, each of which yielded isolates from both CSF and blood. For each of the 23 studies we first calculated the C_{50} value (the number of serogroups responsible for 50% of all CSF isolates or of all blood isolates) and then computed the difference in C_{50} values for each matched pair of CSF and blood. When averaged over 23 studies, the mean difference was only 0.17 serogroups (with a standard deviation of 1.1) (data not shown).

In contrast, there was a difference in serogroup diversity as a function of age. As illustrated for European studies in figure 1 *(left),* the diversity of serogroups found within blood or CSF seems to be consistently less for young children than for older children and adults. To further explore this, we calculated the C_{50} values for each of 16 data sets from any region that involved examination of isolates from the same source from both age groups (figure 1, *right*). The C_{50} value for younger children was greater than that for the older children and adults in 13 of 16 data-set pairs ($P = .006$ by Wilcoxon signed rank test), including 7 of 8 blood data-set pairs and 6 of 8 CSF data-set pairs. This indicates that fewer serogroups are responsible for most bacteremic disease and meningitis in young children, compared with the number of serogroups causing the same diseases in older children and adults.

Contribution of vaccine serogroups to specific disease manifestations. In young children, 7-V serogroups constitute >35% of isolates from blood, CSF, MEF, or specimens (blood and pleural fluid) from patients with pneumonia in each region (figure 2), with the sole exception of CSF isolates in Asia. Serogroups contained in 9-V and 11-V account for at least 60% of all isolates from each source in each region, again with the exception of CSF isolates in Asia. This suggests that a highly effective 9-V or 11-V could make a substantial impact on every major manifestation of pneumococcal disease in each region.

To determine whether that impact would be potentially greater for one disease manifestation than for another, we identified the subset of studies yielding isolates from ⩾2 clinical sites and assessed the proportion of vaccine serogroups from each site. For all 3 vaccine formulations, for each age group, vaccine serogroups are isolated significantly less often from CSF than from the other clinical sites (blood, MEF, or blood/pleural fluid from pneumonia patients; $P < .05$ in each case)—except 7-V serogroups, which show no statistically significant difference in CSF and MEF isolates. Serogroups in 7-V, 9-V, and 11-V cause relatively more pneumonia than meningitis (7-V: OR, 2.9; 95% CI, 1.9–4.5; 9-V: OR, 2.6; 95% CI, 1.7–4.2; 11-V: OR, 3.1; 95% CI, 1.9–5; $P = .001$ in each case). Serogroups in 9-V and 11-V cause relatively more otitis media than meningitis (serogorup 9-V: OR, 0.6; 95% CI, 0.4–0.8; 11-V: OR, 0.4; 95% CI, 0.3–0.6; $P = .001$ in both cases). Serogroups in 7-V, 9-V, and 11-V cause relatively more bacteremic disease than meningitis (7-V: OR, 1.3; 95% CI, 1.1–1.6, $P < .01$; 9-V: OR, 1.7; 95% CI, 1.2–2.4, $P = .001$; 11-V: OR, 2.1; 95% CI, 1.5–3, $P = .001$).

The overall trend is illustrated in figure 3 *(top),* which shows that a slightly lower percentage of 9-V serogroups was found in CSF isolates than in blood isolates in 11 of the 13 studies in which serogroups of both isolates were described (overall $P < .001$).

In addition, 11-V appears to contain a markedly higher percentage of MEF serogroups than does 9-V (figure 2). However, because only 3 studies showed 11-V serogroups in both MEF

Table 4. Pneumococcal serogroups most commonly isolated from clinical sites in various regions.

Population and region	1st	2d	3d	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th
Young children, blood isolates																
United States and Canada																
Serogroup	14	6	19	18	4	9	23	12	7	1	15	3	11	10	16	2
% of total isolates (n = 3543)	28.9	16.2	12.9	8.3	6.9	6.6	6.4	2.1	1.3	0.9	0.9	0.8	0.9	0.7	0.5	0.5
Asia																
Serogroup	1	19	5	14	6	9	18	7	23	31	15	16	12	3	4	2
% of total isolates (n = 590)	15.1	13.2	10.8	8.3	7.8	5.1	4.8	4.4	3.7	3.2	3	2.7	2.6	1.5	1.5	1.2
Europe																
Serogroup	14	19	6	23	18	9	1	4	24	5	7	3	33	15	20	21
% of total isolates (n =723)	17.9	15.8	15.4	9.4	9	6.1	5.8	5	4.8	4.7	4.3	3.2	2.9	1	1	1
Young children, CSF isolates																
United States and Canada																
Serogroup	6	14	19	18	23	4	9	8	10	12	34	3				
% of total isolates (n = 470)	25.9	19.8	12.1	9.8	9.4	3.9	3.3	2.6	2.6	2.6	2.6	1.4				
Asia																
Serogroup	2	5	7	12	6	27	1	14	23	15	3	19	8	18	4	46
% of total isolates (n = 345)	16.3	14.4	9.9	8	7.5	7.3	6.3	5.5	5.4	3.8	3.4	2.9	2.8	2.5	1.8	1.6
Africa																
Serogroup	1	14	19	12	6	5	9	20	7	18	4	29	45	46	2	25
% of total isolates (n = 181)	23.2	13.3	8.8	6.8	6.6	6.1	5.7	5.7	4.7	4.4	3.4	3.4	3.4	3.4	2.9	2.6
Europe																
Serogroup	6	14	19	18	9	23	7	4	15	3	1	24	8	5	3	27
% of total isolates (n = 333)	19.2	14.7	11.8	11.1	8.7	7.7	6.6	5.6	3.1	2.7	2.4	2.4	2.3	2	1.8	1.8
Latin America																
Serogroup	6	14	5	18	23	1	19	9	7	4	10	22	24	3	12	20
% of total isolates (n = 1083)	17	13	9.4	7.4	7.1	7	6.9	3.7	2.7	2.4	2	1.9	1.9	1.6	1.5	1.5
Oceania																
Serogroup	6	14	5	7	2	46	23	8	18	12	19	45	10	33	24	27
% of total isolates (n = 118)	14.4	14.4	9.3	8.4	5.1	5.1	5.1	5.1	4.2	4.2	4.2	3.4	3.4	3.4	1.7	1.7
Young children, MEF isolates																
United States and Canada																
Serogroup	19	6	23	14	3	18	9	15	4	1	7	11	22	8	10	35
% of total isolates (n = 2532)	24	12.7	12.5	10.8	8.6	4.9	3.5	2.9	2.8	2.2	2	1.9	1.5	1.4	1.4	1.1
Europe																
Serogroup	19	6	14	23	3	9	18	7	1	15	11	5	22	10	8	4
% of total isolates (n = 2183)	22.1	16.9	14.5	11.3	7.8	4.8	2.7	2.3	2.3	2.2	1.9	1.4	0.8	0.6	0.6	0.5
Young children with pneumonia, blood or PF isolates																
Latin America																
Serogroup	14	1	5	6	3	19	9	7	23	15	21	18	8	12	4	16
% of total isolates (n = 561)	32.1	15.1	13.7	7.2	5.9	4.5	4.2	4.1	4	2.2	1.5	1.1	0.7	0.4	0.4	0.4
Older children and adults, blood isolates																
Asia																
Serogroup	1	19	3	5	14	23	7	6	12	9	4	10	34	16	17	18
% of total isolates (n = 564)	14.7	8.7	8.6	7.2	7.2	6.2	5.8	5.5	5.1	3.7	3.4	3.4	1.8	1.6	1.4	1.2
Europe																
Serogroup	1	14	9	4	3	7	6	19	23	8	12	5	18	22	20	11
% of total isolates (n = 8376)	9.4	9.3	9.1	8.4	8.1	7.4	6.7	6.2	5.1	4.9	3.9	3.4	3.4	2.1	1.9	1.7
Older children and adults, CSF isolates																
Europe																
Serogroup	6	19	9	23	3	14	7	18	4	12	8	24	1	10	22	15
% of total isolates (n = 1714)	10.9	8.3	8.1	7.7	7.5	7.2	6.8	6.2	5.5	4.3	4.1	3.3	3.1	2.5	2	2.4

NOTE. Data are weighted averages in regions where there were ⩾3 studies per indicated category. MEF, middle-ear fluid; PF, pleural fluid.

and blood isolates, no statistically significant difference in vaccine coverage by isolate source could be established.

Vaccine serogroups in young children versus older children and adults. The accompanying (preceding) article indicated that vaccine serogroups account for a higher proportion of invasive disease isolates from young children than of isolates from older children and adults [6]. To determine whether this effect was restricted to CSF or blood isolates only, we analyzed the 14 studies that isolated each of the 7 serogroups in 7-V and that examined isolates from CSF, blood, or samples from pneumonia patients in both age groups.

As depicted in figure 3 *(bottom),* in 13 of those studies the serogroups represented in the 7-V formulation are found less often in the older age group than in the younger; overall a highly significant finding ($P < .001$). This suggests that, for each invasive isolate source, the vaccines would prevent a relatively

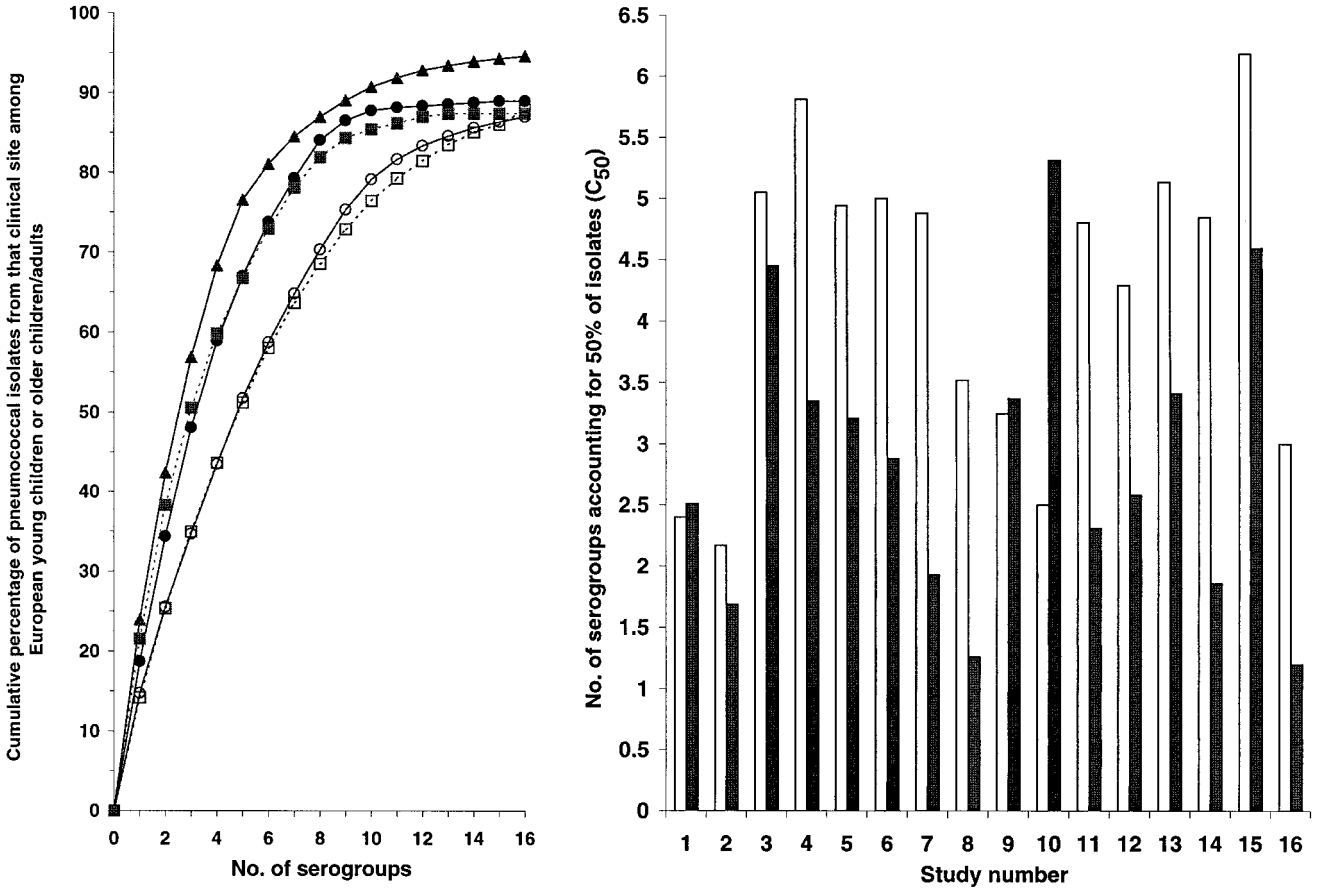

Figure 1. No. of pneumococcal serogroups responsible for increasing percentages of pneumococcal disease, by clinical site of isolation and by geographic region in different age groups. *Left,* For each European study listed in tables 1–3, contribution of each pneumococcal serogroup to all isolations from that site was first expressed as a percentage, percentages were ranked in descending order, and serogroups (first, second, third, etc.) were averaged for all studies in that age grouping and region. Depicted are cumulative percentage of contributions of the first 14–16 serogroups. Black symbols are for younger children and white symbols for older children and adults. Circles (○, ●) represent blood isolates, squares (□, ■) CSF isolates, and triangles (▲) middle-ear-fluid (MEF) isolates. *Right,* 50%-coverage values (C_{50} values) for each study from any region that examined blood or CSF isolates from both age groups: younger children *(black bars)* and older children and adults *(white bars).* Isolates were from blood in studies 1–8 and from CSF in studies 9–16. References for studies are as follows: 1, [21]; 2 and 10, [17]; 3, [19]; 4 and 11, [25] and personal communication (PC), A. Fenoll and J. Casal; 5 and 12, [26]; 6 and 13, [23] and PC, J. Dankert and A. van der Ende; 7, [13]; 8 and 16, PC, G. G. Hogg and J. Strachan; 9, [41]; 14, [50]; and 15, [44].

higher percentage of disease in the younger age group than in the older age group.

Tendencies of individual serogroups to be isolated from a specific clinical source. The vaccine serogroup analyses implied that some individual serogroups probably cause one disease manifestation more than another. To examine this more closely and to minimize potentially confounding differences in inter-study methodology, we focused on those studies whose investigators reported the frequency of isolation of individual serogroups from >1 clinical source.

However, even with this focus, we were concerned that the apparent association of a given serogroup with a specific clinical site may reflect its age-incidence rather than a proclivity for a specific site. For example, meningitis tends to occur at slightly younger ages than the other syndromes [20], and a finding that a specific serogroup is more often isolated from CSF may be simply due to its tendency to be isolated from very young children rather than to a preference for CSF per se. Since most study reports lack sufficient age-specific information, we sought to minimize this factor by identifying each serogroup that consistently showed a tendency to be isolated from a certain clinical site in both young children and older children/adults. We were limited to comparing blood and CSF isolates, since those were the only 2 clinical sites for which there were sufficient data in both age groups.

Figure 4 depicts 2 examples. In both age groups, serogroup 23 was isolated slightly but significantly more frequently from CSF than from blood (for older children and adults $P < .01$,

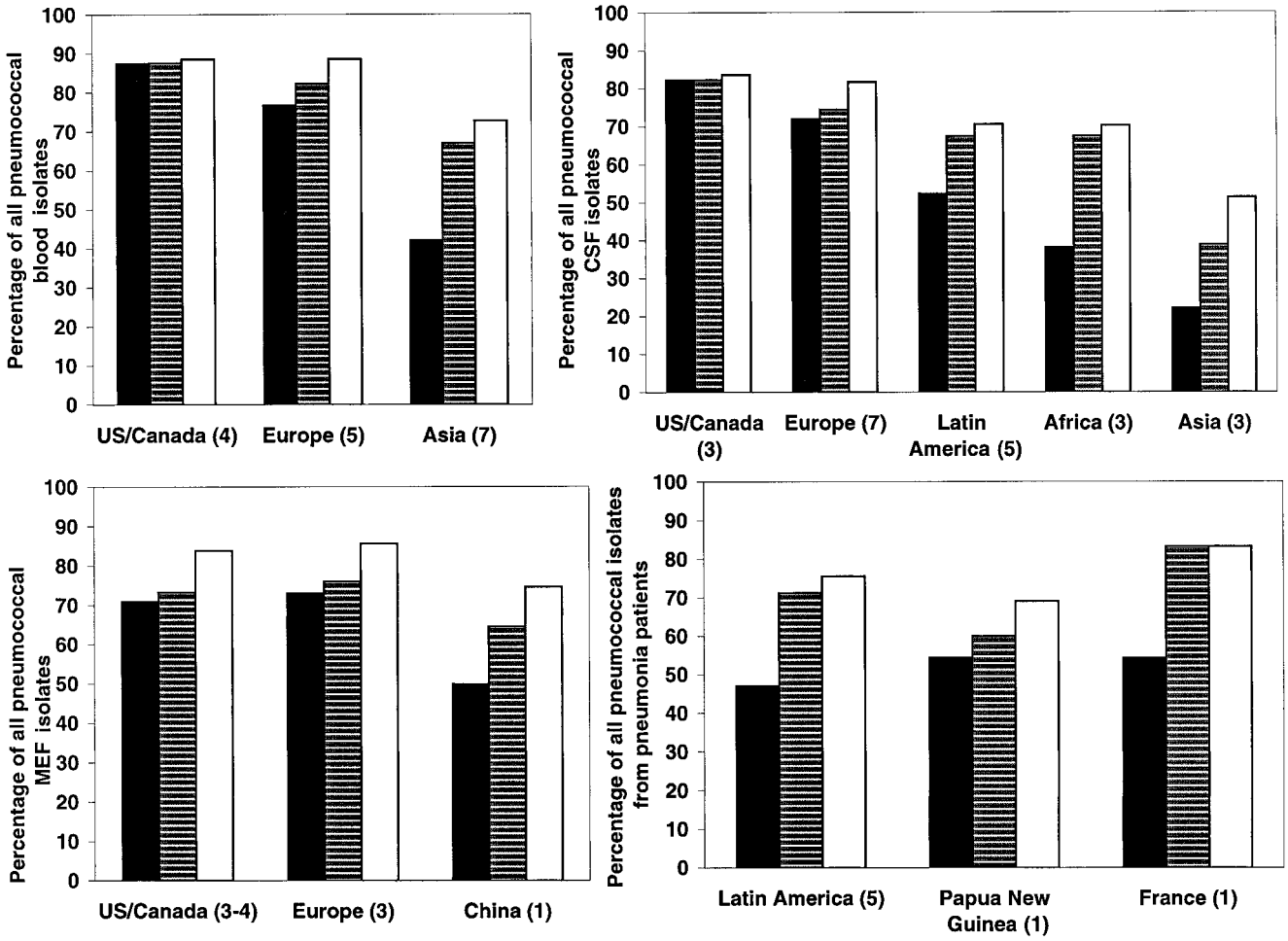

Figure 2. Serogroups contained in 7-V, 9-V, and 11-V as causes of specific manifestations of pneumococcal disease in young children, by clinical site of isolation and disease syndrome. For each study, the amount of disease caused by each set of vaccine serogroups is presented as the percentage of all pneumococcal serogroup isolates in that respective category: blood *(upper left),* CSF *(upper right),* middle ear fluid (MEF; *lower left*), and *(lower right)* specimens (blood and pleural fluid) from patients with pneumonia. Serogroups in 7-V *(black bars),* 9-V *(striped bars),* and 11-V *(white bars)* cause relatively more pneumonia than they do meningitis. Serogroups in 9-V and 11-V cause relatively more otitis media than they do meningitis. Serogroups in 7-V, 9-V, and 11-V cause relatively more bacteremic disease than they do meningitis. For details of *P* values, ORs and CIs, see text; for details of statistical comparison, see Methods. Only study reports listing all serogroups included in a given vaccine formulation for at least 2 disease manifestations were included in this analysis. No. of studies in each country or region is given in parentheses.

Mantel-Haenszel OR [OR], 0.7; 95% CI, 0.6–0.9; for young children, $P < .05$, OR, 0.7; 95% CI, 0.5–0.9]). Likewise, in both groups serogroup 1 was found significantly more often in blood than in CSF (for either older children and adults, $P < .001$, OR, 4.4; 95% CI, 3.1–6.2; for young children, $P < .001$, OR, 3.5; 95% CI, 2.2–5.6). When all studies with a given serogroup are taken together, these findings are statistically significant, but significance was apparent at an individual study level in only a few cases (labeled with an asterisk). Conversely, a few individual studies appeared to show the exact opposite pattern, highlighting the danger of drawing broad conclusions about serogroup preferences from an individual study.

Serogroup 14 was also more often isolated from blood than from CSF ($P < .01$ and $P < .001$ for older and younger age groups, respectively), as was serogroup 4 ($P < .01$ and $P < .05$ for older and younger age groups, respectively). Conversely, serogroup 6 ($P < .001$ for both age groups) and serogroup 10 ($P < .001$ for both age groups) were more often found in CSF rather than in blood. However, clear interpretation of these latter results is complicated by the existence of multiple common serotypes within serogroups 6 and 10.

To examine MEF fluid isolates, our data set consisted only of studies of young children. Figure 5 shows that in this group serogroup 1 was more commonly isolated from blood than from MEF or from CSF ($P = .001$; OR, 3.2; 95% CI, 2.1–4.7; CSF vs. MEF, no statistically significant difference). Serogroup 3 is

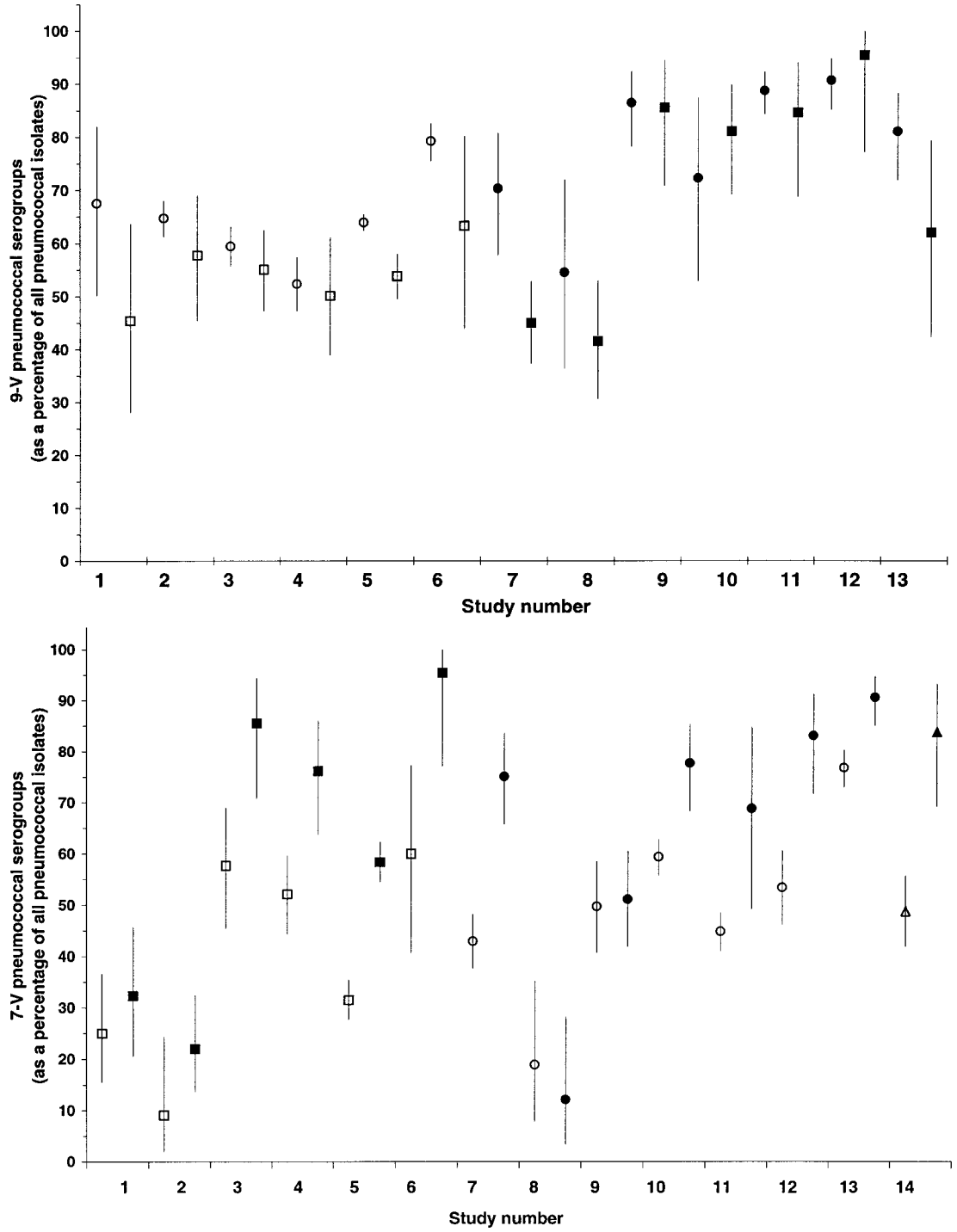

Figure 3. Vaccine serogroups represented in CSF and blood isolates, in different age groups. White symbols represent older children and adults; black symbols represent young children. Circles (○, ●) represent blood isolates, squares (□, ■) CSF isolates, and triangles (△, ▲) isolates from pneumonia patients (blood plus pleural fluid). Percentage of isolates comprising serogroups represented in 9-V *(top)* or 7-V *(bottom)* was calculated (along with 95% CIs) for each study. *Top,* 9-V vaccine coverage by isolate source. Only studies that reported all 9 vaccine serogroups (with possible exception of serogroup 5—see Methods) in both CSF and blood isolates in a single age group were analyzed. References for studies are as follows: 1 and 8, [17]; 2 and 9, [26]; 3 and 10, [23] and personal communication (PC), J. Dankert and A. van der Ende; 4, [33]; 5, [37]; 6 and 12, PC, G. G. Hogg and J. Strachan; 7, [16]; 11, [11]; 13, [29] and PC, Diana Martin. *Bottom,* 7-V vaccine coverage by age group. Only studies that reported all 7 serogroups for both age groups from a single isolate source (CSF, blood, or specimens from patients with pneumonia [blood and pleural fluid] were included. In each case the percentages were significantly greater ($P < .001$) for young children than for older children and adults. References for studies are as follows: 1, [39]; 2 and 8, [17]; 3 and 10, [26]; 4 and 11, [23] and PC, J. Dankert and A. van der Ende; 5, [44]; 6 and 13, PC, G. G. Hogg and J. Strachan; 7, [21]; 9, [19]; 12, [13]; and 14, [14].

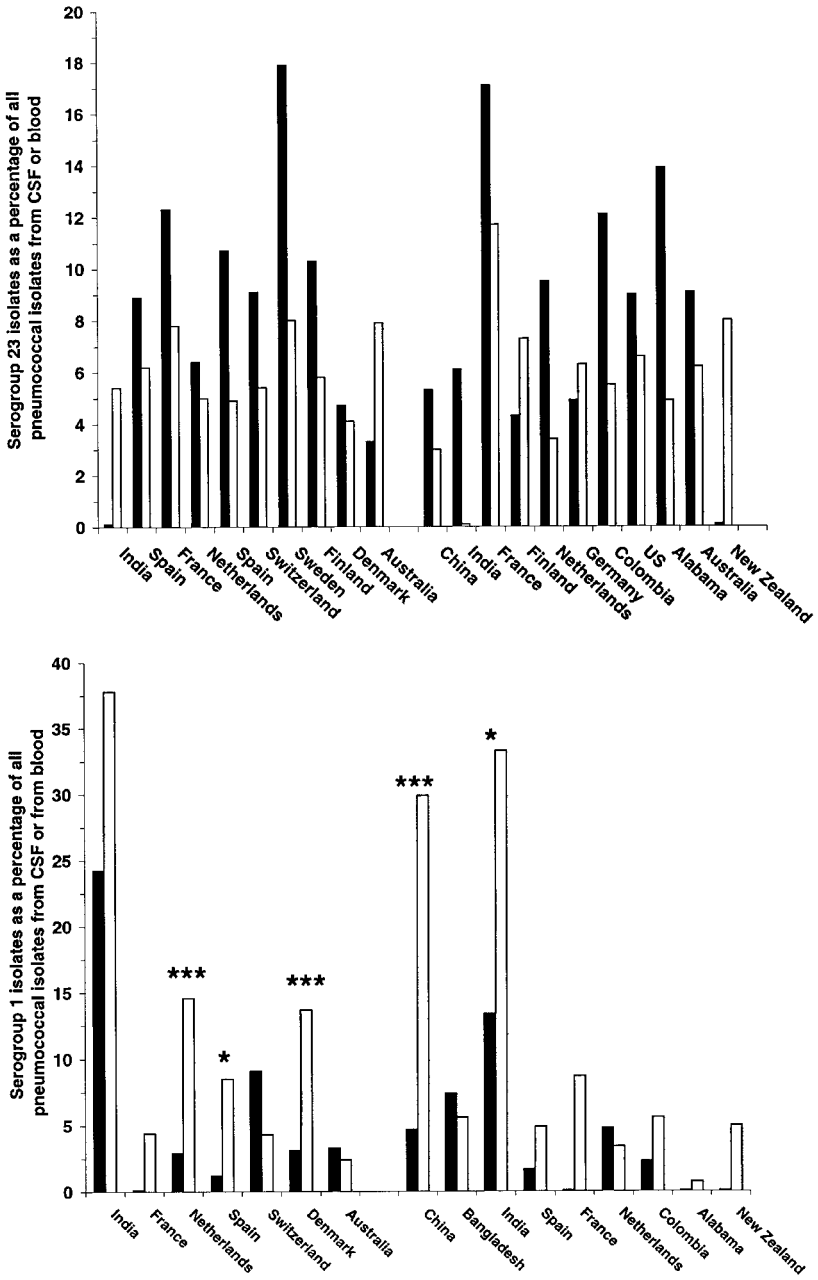

Figure 4. Relative tendencies for serogroup 1 and 23 to be isolated from blood vs. CSF in different age groups. Bars represent percentage of all pneumococcal isolates from blood *(white bars)* or CSF *(black bars)* that were of serogroups 23 *(top)* and 1 *(bottom)* for each study in older children/adults (left) and younger children *(right)*. Only studies reporting both blood and CSF isolates of the specific serogroup were included in this analysis. Serogroup 1 is more likely to be isolated from blood than from CSF; serogroup 23, the reverse: a single asterisk (*) denotes $P < .05$; double asterisks (**), $P < .01$; and triple asterisks (***), $P < .001$. For ORs and CIs, see text; for details of statistical comparison, see Methods. References for serogroup 1 are as follows: India, [17]; France, [26]; Netherlands, [23] and personal communication (PC), J. Dankert and A. van der Ende; Spain (older children and adults only), [33]; Switzerland, [34]; Sweden, [35]; Denmark, [37]; Australia, PC, G. G. Hogg and J. Strachan; China, [16]; Bangladesh, [15]; Spain (young children only), [25] and PC, A. Fenoll and J. Casal; Colombia: [27]; Alabama, [11]; New Zealand, [29] and PC, D. Martin. References for serogroup 23 (older children and adults): India, [17]; Spain (a), [25] and PC, A. Fenoll and J. Casal; France, [26]; Netherlands, PC, J. Dankert and A. van der Ende [23]; Spain (b), [33]; Switzerland, [34]; Sweden, [35]; Finland (older children and adults only), [36]; Denmark, [37]; Australia, PC, G. G. Hogg and J. Strachan; China, [16]; Finland (young children only), [22]; Germany, [24]; Colombia, [27]; United States [12]; Alabama, [11]; New Zealand, [29] and PC, D. Martin.

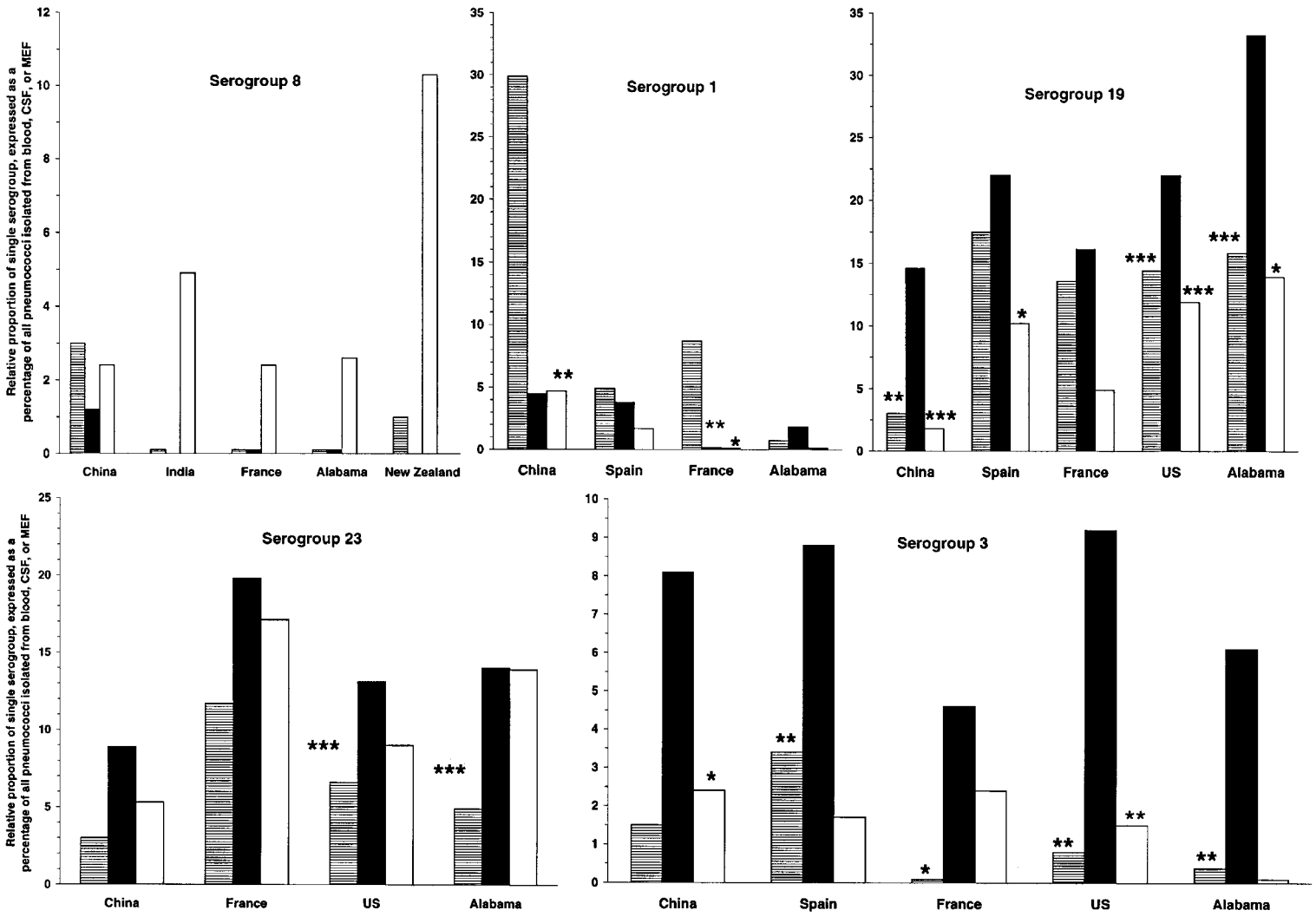

Figure 5. Relative tendencies for specific serogroups to be isolated from middle ear fluid (MEF) vs. other clinical sites in young children. For each study, the amount of disease caused by serogroups 8 *(top left)*, 1 *(top middle)*, 19 *(top right)*, 23 *(lower left)*, and 3 *(lower right)*, respectively, in young children is presented as percentage of all pneumococcal isolates from blood (striped bars), CSF *(white bars)*, or MEF *(black bars)*. Only studies reporting specific serogroup of MEF isolates and of isolates from at least 1 other clinical site were included in this analysis, with exception of studies in India and New Zealand for serogroup 8, in which there were no MEF data. A single asterisk (*) denotes $P < .05$; double asterisks (**), $P < .01$; and triple asterisks (***), $P < .001$ For details of P values, Mantel-Haenszel ORs and 95% CIs, see text; for details of statistical comparison, see Methods. References for serogroups 3, 8, and 19 are as follows: China, [16]; Spain, [25] and personal communication, A. Fenoll and J. Casal; France, [26]; United States, [12]; Alabama, [11]. References for serogroups 1 and 23 are given in the legend to figure 4.

more frequently isolated from MEF than from CSF (P = .001; OR, 5.1; 95% CI, 2.9–9) or blood (P = .001; OR, 6.8; 95% CI, 4.6–10; CSF vs. blood, no statistically significant difference). The tendency for serogroup 3 to be isolated from MEF largely explains the earlier observation (figure 2) that serogroups in 11-V (which includes serogroup 3) represent a greater proportion of MEF isolates than do serogroups in 9-V (which contains serogroup 1 but not 3) or in 7-V.

Figure 5 also shows that serogroups 19 and 23 were more commonly isolated from MEF than from the other sites. Serogroup 19 is more frequently isolated from MEF than from CSF (P = .001; OR, 2.8; 95% CI, 2–3.8) or blood (P = .001; OR, 1.7; 95% CI, 1.4–2.1) and is isolated from blood slightly more frequently than from CSF (P < .05; OR, 1.3; 95% CI, 1.0–1.7). Serogroup 23 is more frequently isolated from MEF than from CSF (P < .05; OR, 1.4; 95% CI, 1–2) or blood (P = .001; OR, 1.8; 95% CI, 1.4–2.3). However, the paucity of MEF data for older children and adults made it impossible to determine whether serogroups 3, 19, and 23 were also more commonly isolated from that site among patients in that age group. Finally, among young children serogroup 8 was more commonly isolated from CSF than from blood (P < .01; OR, 3.8; 95% CI, 1.4–10.4) or MEF (P < .05; OR, 3.5; 95% CI, 1.1–10.7; blood vs MEF, no statistically significant difference). In isolates from older children and adults, however, serogroup 8 was not found at a significantly different rate in CSF and blood (P = .2), a finding that is difficult to interpret.

Discussion

These analyses indicate that the serogroups represented in conjugate vaccine formulations largely reflect the main disease-causing serogroups for each major clinical manifestation of pneumococcal infection in each region of the world. Since the serogroups in the conjugate formulation were originally chosen on the basis of studies of mostly bacteremic disease in young children in United States and Europe, it is valuable to know that these vaccines, especially the 9-V and 11-V, would also potentially address the major serogroups responsible for otitis media, meningitis, and pneumonia on a global basis.

We also found that a relatively small number of pneumococcal serogroups are responsible for most cases of each disease syndrome in young children in each region. A slightly but consistently larger number of serogroups are responsible for most cases of bacteremic disease and meningitis in older children and adults.

These analyses also support previous findings that most serogroups appear to be isolated with similar frequency from each normally sterile site. A few serogroups, however, are consistently isolated more frequently from 1 specific site, even across geographic regions and in different age groups. Although this finding was not unanticipated, previous studies of this topic were limited to relatively small, country-specific analyses in which apparent differences might simply reflect the particular epidemiological conditions or study methodologies used in a particular country, making it difficult to generalize those findings. In fact, as figures 4 and 5 show, even those differences in isolation site that are deemed statistically significant when averaged across several studies are not always observed within every single study. Whether these represent true population differences can be answered only by studies in which methodologies are strictly controlled and comparable between sites.

To minimize study-to-study methodological differences, we restricted our analyses of serogroup tissue "tropisms" to only those study reports listing isolates from >1 sterile site and assessed the relative tropisms within each study on an individual basis prior to analysis. The general tendencies described in these analyses might help investigators focus on certain serogroups when seeking to elucidate the pathophysiological and molecular bases for these "tropisms." Such studies might compare various properties of 2 serotypes, such as 1 and 23F, with apparently opposite predilections for blood and CSF. Characteristics of individual serogroups that might explain these tropisms could include an intrinsic ability to rapidly achieve high concentrations in blood or some feature of the chemistry of the capsule or other surface structures that mediate adherence and/or passage through the blood-brain barrier.

In this context, it should be noted that none of the most prominent serotypes is exclusively found in one clinical site or another, that is, all seem to have the potential to invade each of the normally sterile sites and to cause disease from those sites. Whether the same is true for the more minor serotypes remains unclear. This does not mean, however, that each serotype has the ability to invade all sterile sites by every possible route. For example, some serotypes that only occasionally appear in the CSF could conceivably be incapable of crossing an intact blood-brain barrier (e.g., one that has not been damaged by trauma) in a well-nourished individual.

Even with the advantages of a multistudy comparison, it is important to recognize a major limitation of this survey: the difficulties in controlling for variables in study design and population that might influence the apparent frequency of isolation from different clinical sites. Foremost among these variables are the precise ages of the respective study populations. For example, within the "younger children" age group, it is not clear whether the pneumococcal serogroups responsible for otitis media differ from those causing meningitis in age ranges narrower than we could assess.

For this reason, we have greater confidence in conclusions regarding serotypes and serogroups that show strong preferences for blood or for CSF in both young children and older children and adults, since this would seem to minimize the potentially confounding influence of the age variable. In contrast, the paucity of information about otitis media in adults

precludes any definitive conclusions about the serogroup tendencies for that disease manifestation.

A second important variable may lie in differences in various study populations in the threshold of disease severity that prompts sterile-site culturing. This may not be a major factor for patients with meningitis, but for reasons outlined in the accompanying article [6], the spectrum of clinical disease from which bacteremic pneumococcal isolates are derived probably varies in different regions, thereby influencing which serotypes were detected.

It would be interesting to learn, for example, whether some serotypes are intrinsically highly virulent, regardless of the clinical site from which they are isolated. In this regard, a revealing comparison might be between those serotypes with a predilection for causing especially severe septicemia and those with a tendency to cause meningitis. To undertake such an analysis would necessitate more detailed clinical information than usually is found in the studies analyzed here.

Pneumonia is perhaps the most important manifestation of pneumococcal disease, but except for investigations in Latin America, very few studies specifically identified isolates as being from patients with pneumonia, a circumstance prompting caution about generalizations from that data set. In addition, it is possible that serotype information derived primarily from blood isolates does not necessarily reflect what would be found following lung aspiration, a more direct method of assessing the serotypes responsible for pneumonia. Also worth examining is whether assays other than cultures (e.g., PCR and latex agglutination) might reveal differences in the relative distribution of serogroups. Each of the above considerations emphasizes the value of development and use of standardized study methodologies and reporting procedures [6].

Overall, these analyses may offer some implications for conjugate vaccine formulation and use. It has been previously suggested that "developing country–specific" vaccine formulations may be necessary to prevent a major portion of the most serious pneumococcal disease (i.e., pneumonia and meningitis) in developing countries [9]. However, on the basis of available data in this and the accompanying article [6], it appears that the conjugate formulations epidemiologically relevant for the industrialized world, especially 9-V and 11-V, have the potential to prevent a large portion of the cases of pneumococcal pneumonia and meningitis in developing countries.

If there is little epidemiological reason to design a "developing country–specific" formulation, then manufacturers (and developing-country consumers) will potentially benefit from minimization of the number of vaccine development programs, from the economies of vaccine production on a large scale, and from avoiding the need for parallel inventories. These analyses also confirm the epidemiological relevance of testing current formulations in developing as well as industrialized countries [7]. These elements have been critical in allowing manufacturers to offer a tiered pricing structure for vaccines sold to both types of countries [58].

At the same time, the substantial overlap between the set of serotypes isolated from MEF in industrialized countries and from invasive disease sites in developing countries underscores another important relationship. Therapeutic practices for otitis media in industrialized countries that inadvertently lead to antibiotic-resistant serotypes may ultimately have much more serious implications elsewhere, since the same resistant serotypes also have the potential to cause meningitis and other forms of invasive disease.

Since the vast majority of resistant serotypes are represented in 7-V [6], the routine use of conjugate vaccines to prevent invasive disease and otitis media may conceivably have a broad impact on the epidemiology of pneumococcal antimicrobial resistance beyond the vaccinated population. This impact may even be augmented if conjugate vaccines given to infants are shown to prevent prolonged nasopharyngeal carriage of those pneumococci most associated with resistance [59–61], further decreasing opportunities for antibiotic resistance to develop.

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