bodies and dexamethasone in experimental *Haemophilus* meningitis. J Clin Invest 1991;88:2003–11.
28. Syrogiannopoulos G, Olsen KD, Reisch JS, McCracken GH Jr. Dexamethasone in the treatment of experimental *Haemophilus influenzae* type b meningitis. J Infect Dis 1987;155:213–9.
29. Quagliarello V, Scheld WM. Bacterial meningitis: pathogenesis, pathophysiology, and progress. N Engl J Med 1992;327: 864–72.
30. Ashwal S, Stringer W, Tomasi L, et al. Cerebral blood flow and carbon dioxide reactivity in children with bacterial meningitis. J Pediatr 1990;117:523–30.
31. Paulson OB, Broderson P, Hansen EL, et al. Regional cerebral blood flow, cerebral metabolic rate of oxygen and cerebrospinal acid-base variables in patients with acute meningitis and with acute encephalitis. Acta Med Scand 1974;196: 191–8.
32. Tureen JH, Dworkin RJ, Kennedy SL, Sachdeva M, Sande MA. Loss of cerebrovascular autoregulation in experimental meningitis in rabbits. J Clin Invest 1990;85:577–81.
33. Minns RA, Engleman HM, Stirling H. Cerebrospinal fluid pressure in pyogenic meningitis. Arch Dis Child 1989;64: 814–20.

Pediatr Infect Dis J, 1995;14:503–10
0891-3668/95/$03.00/0

Vol. 14, No. 6
Printed in U.S.A.

Potential interventions for the prevention of childhood pneumonia: geographic and temporal differences in serotype and serogroup distribution of sterile site pneumococcal isolates from children—implications for vaccine strategies

DAVID H. SNIADACK, MD, BENJAMIN SCHWARTZ, MD, HARVEY LIPMAN, PHD, J. BOGAERTS, MD, JAY C. BUTLER, MD, RON DAGAN, MD, GABRIELA ECHANIZ-AVILES, MSC, NELLIE LLOYD-EVANS, MD, A. FENOLL, MD, NABIL I. GIRGIS, MD,* JORGEN HENRICHSEN, MD, KEITH KLUGMAN, MD, DEBORAH LEHMANN, MBBS, MSC, AINO K. TAKALA, MD, J. VANDEPITTE, MD, SANDY GOVE, MD, MPH AND ROBERT F. BREIMAN, MD

***Streptococcus pneumoniae* is a leading cause of fatal bacterial pneumonia in young children.**

Accepted for publication March 16, 1995.
From the Centers for Disease Control and Prevention, Atlanta, GA (DHS, BS, HL, JCB, RFB); Centre Hospitalier de Kigali, Kigali, Rwanda (JB); Ben Gurion University, Beer Sheva, Israel (RD); Instituto Nacional de Salud Pública, Cuernavaca, Mexico (GE); Medical Research Council Laboratories, Banjul, The Gambia (NLE); Centro Nacional de Microbiología, Majadahonda, Madrid, Spain (AF); Biomedical Research Center for Infectious Diseases, Cairo, Egypt (NG); Staten Seruminstitut, Copenhagen, Denmark (JH); South African Institute for Medical Research, Johannesburg, South Africa (NK); Papua New Guinea Institute of Medical Research, Goroka, Papua New Guinea (DL); National Public Health Institute, Helsinki, Finland (AKT); Katholieke Universiteit Leuven, Leuven, Belgium (JV); and the WHO Programme for the Control of Acute Respiratory Infections, Geneva, Switzerland (SG).
* Deceased 1994.
Key words: Pneumococcus, serotype, serogroup, conjugate vaccine.
Address for reprints: Robert F. Breiman, Mailstop C-09, Division of Bacterial and Mycotic Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333.

Pneumococcal polysaccharide vaccines have not been promoted for use in young children because many constituent serotypes are not immunogenic in children <2 years old. Conjugating pneumococcal polysaccharide epitopes to a protein carrier would likely increase vaccine immunogenicity in children. We reviewed published and unpublished pneumococcal serotype and serogroup data from 16 countries on 6 continents to determine geographic and temporal differences in serotype and serogroup distribution of sterile site pneumococcal isolates among children and to estimate coverage of proposed and potential pneumococcal conjugate vaccine formulas. The most common pneumococcal serotypes or groups from developed countries were, in descending order, 14, 6, 19, 18, 9, 23, 7, 4, 1 and 15. In developing countries the order was 6, 14, 8, 5, 1, 19, 9, 23, 18, 15 and 7. Development of customized heptavalent vaccine formulas, one for

use in all developed countries and one for use in all developing countries, would not provide substantially better coverage against invasive pneumococcal disease than two currently proposed heptavalent formulas. An optimal nanovalent vaccine for global use would include serotypes 1, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F. Geographic and temporal variation in pneumococcal serotypes demonstrates the need for a species-wide pneumococcal vaccine.

INTRODUCTION

Streptococcus pneumoniae is the leading cause of fatal bacterial pneumonia in developing countries.[1–5] Pneumonia accounts for up to 30% of all deaths in children <5 years old from developing countries,[6] and 75% of all pneumonia deaths in children <5 years old occur in infants.[7] Case management, when optimally applied, has been effective in reducing childhood pneumonia-related mortality by 50% and overall child mortality by 25%.[8] However, the spread of drug-resistant pneumococcal strains[9, 10] may reduce the usefulness of case management. Immunization with an effective pneumococcal vaccine is the optimal approach to reduction of mortality caused by *S. pneumoniae*.

Antigenic differences among pneumococcal capsular polysaccharides are the basis for typing *S. pneumoniae*. Thus far 84 pneumococcal serotypes have been identified. The basis for the current 23-valent pneumococcal polysaccharide vaccine is that antibodies against specific pneumococcal capsular polysaccharide antigens provide protection against infection with that serotype.[11] However, many polysaccharide antigens are not immunogenic in children <2 years old because, as T cell-independent antigens, they are not efficiently processed in immune systems that are not fully mature.[12–15] Hence available pneumococcal polysaccharide vaccines have not been promoted for use among young children in whom the incidence of pneumonia-related death is highest. To overcome this problem new vaccines are being developed in which pneumococcal capsular polysaccharides are conjugated to protein carriers. Two formulas have been proposed which are targeted against common pediatric serotypes. Formula A includes serotypes 4, 6B, 9V, 14, 18C, 19F and 23F; Formula B includes serotypes 1, 5, 6B, 14, 18C, 19F and 23F.

The effectiveness of potential pneumococcal conjugate vaccine formulas to prevent pneumococcal disease in children depends in part on the proportion of infections caused by serotypes included in the vaccine. We reviewed published and unpublished pneumococcal serotype and serogroup data from 16 countries on 6 continents[16–27] to identify potential geographic and temporal variations in pneumococcal serotype and group distribution in children, estimate the serogroup coverage of proposed and other potential conjugate vaccines and determine an optimal conjugate vaccine formula.

METHODS

Published and unpublished pneumococcal serotype or serogroup data were obtained from 19 studies in 16 countries (Table 1) in which isolates from blood, cerebrospinal fluid (CSF), transtracheal aspirate, lung aspirate and pleural fluid were collected from children. Unpublished data were collected from 9 of the 19 studies. Fourteen studies included only data from children <5 years old; the other 5 studies included data from some children between 5 and 15 years of age.

TABLE 1. Contributors to the pneumococcal serotype and serogroup prevalence survey

Site	Author	Age (Years)	Years	Sample	Source
United States	Butler	< 5	1977–1994	3523	B,C,P
Mexico	Echaniz*	< 5	1992–1993	120	B,C
Brazil	Taunay et al.[16]	< 2	1977–1988	308	C
Uruguay	Mogdasy et al.[17]	< 5	1987–1989	48	B
Spain	Fenoll	< 5	1979–1993	167	B,C,P,T
Belgium	Vandepitte	< 5	1991	77	B,C
Finland	Eskola	< 2	1985–1989	235	†
Denmark	Henrichsen	< 14	1991–1992	164	B,C
South Africa	Klugman	< 5	1987–1991	1138	B,C
Rwanda	Bogaerts et al.[21]	< 15	1984–1990	130	B,C
Gambia	Lloyd-Evans	< 5	1991	59	B,C,A,P
Egypt	Guirguis et al.[22]; Khallaf	< 6	1977–1978;	59	C
			1992	27	B
Israel	Dagan	< 5	1988–1991	133 Jews	
				91 Arabs	B,C
Pakistan	Mastro et al.[20]	< 5	1986–1989	87	B
			1989–1990	81	B
Papua New Guinea	Gratten et al.[25,26]	< 5	1980–1987‡	151	B,C
Australia	Hansman[24]	Children	1970–1979	219	B,C

* Unpublished materials.

† All sterile sites excluding middle ear fluid.

‡ PNG data submitted by Dr. Lehmann were obtained from two studies published by Gratten et al.[25,26]

B, blood; C, cerebrospinal fluid; P, pleural fluid; T, transtracheal aspirate; A, lung aspirate.

Isolates from vaccinated children (known only for the United States) were excluded from analysis.

The primary level of analysis of these data was of pneumococcal serotypes or serogroups that are identified by pneumococcal antisera. Pneumococcal serogroups include several antigenically similar serotypes that cannot be distinguished by routinely available antisera (e.g. serogroup 6 includes serotypes 6A and 6B), whereas serotypes include a single antigen (e.g. serotypes 1, 5 and 14). An additional set of antisera, factoring sera, is required further to type isolates belonging to a serogroup. Because the majority of studies did not use factoring serum for differentiation of serotypes among serogroups, data were analyzed for serotype or serogroup prevalence rather than serotype prevalence alone.

The possibility that age or specimen type might influence serotype or serogroup distribution was evaluated when individual studies reported appropriate data. The prevalence of individual serotypes or groups was determined by age (<2 years *vs.* 2 to 4 years) in five countries and by specimen source (blood *vs.* CSF) in six countries.

To determine whether serotype or group prevalence of sterile site isolates are stable over time, annual changes in serotype or group distribution were analyzed in two countries, the United States and South Africa, which collected data for at least 5 consecutive years.

To obtain estimates of serotype or group prevalence in developed and developing countries, we determined 25% trimmed means for each serotype or group in each country group and then corrected to 100%. This process calculates mean values from the middle 50% of the data, "trimming" the upper and lower 25% of data points, thereby reducing the impact of outlying data. We refer to the prevalence thus obtained as the corrected trimmed mean prevalence (CTMP). The developed country group included the United States, Belgium, Denmark, Finland and Spain. The developing country group included Brazil, Uruguay, Rwanda, The Gambia, Egypt, Pakistan and Papua New Guinea (PNG). Data from South Africa, Israel and Australia were excluded from either group because studies from these countries included sizable populations with characteristics of developed and developing countries. Data from more than one study within a country (i.e. Pakistan, Egypt and PNG) were combined when similar enrollment criteria were used.

On the basis of country group CTMPs we determined several potential heptavalent and nanovalent pneumococcal conjugate vaccine formulas that would provide the greatest serogroup coverage in developed and developing countries. Global CTMPs were used to determine an optimal vaccine formula for global use. For each potential vaccine formula, the most commonly occurring serotype within a serogroup was selected for inclusion. Potential formulas included: (1) a combination of the nine serotypes included in the two currently proposed vaccine formulas (Formula A + B vaccine); (2) vaccines incorporating the seven and nine most common serotypes in developed or developing country groups (Developed and Developing Custom 7 and Custom 9 vaccines; (3) the nine most common serotypes globally (Global 9 vaccine).

Serogroup coverage in developed and developing country groups was determined for proposed and potential vaccine formulas by summing the CTMPs of serotypes and groups corresponding to the constituent serotypes of the respective vaccine. Thus determination of serogroup coverage assumes that all serotypes within any serogroup confer serogroup-wide protection. In fact this is likely to be true only for serogroup 6, in which the antigenic similarities between serotypes 6A and 6B are such that serogroup-wide protection occurs after immunization with serotype 6B antigen.[11] For other serogroups cross-protection appears to be very limited.

To determine the extent to which serogroup coverage overestimates true coverage, we compared serogroup coverage with serotype-related coverage of the potential vaccine formulas using data from countries in which factoring sera were used to identify serotypes within groups. In determining serotype-related coverage we assumed that of all serotypes contained in the two formulas, only 6B had cross-reactivity with another serotype (i.e. 6A).

The statistical significance of differences in serogroup prevalence between age groups and specimen types within countries was determined using Yates' corrected chi square on Epi-Info[16] software. Fisher's exact test was used when the expected number of isolates of a particular category from children was <5. The significance of differences in the prevalence of serotypes or groups by year within the United States and South Africa was determined with a chi square test of independence. If either country exhibited significant variation of serotype or group distribution by year, additional chi square tests for independence were performed for each year. The significance of differences in coverage of potential vaccine formulas within countries was determined using McNemar's test. All *P* values are two tailed.

RESULTS

Serotype or group prevalence by country group. The 10 most common serotypes or groups associated with invasive pneumococcal disease in children from developed countries are, in descending order, 14, 6, 19, 18, 9, 23, 7, 4, 1 and 15 (Table 2). The most common serotypes or groups among children in devel-

TABLE 2. Serotype and serogroup prevalence by country and CTMP by country group

Country	Serogroup Prevalence (%)																	
	1	4	5	6	9	14	18	19	23	2	7	12	15	16	31	45	46	Other
Developed																		
United States	1.1	6.7	0.2	17.1	7.2	27.3	9.3	14.2	7.1	0.0	1.6	0.6	1.1	0.3	0.0	0.0	0.1	6.0
Spain	3.0	2.4	7.2	17.4	4.8	2.6	4.8	17.4	15.0	0.6	3.0	0.0	1.8	0.6	0.0	0.6	0.0	8.8
Belgium	5.2	2.6	1.3	7.8	9.0	28.6	9.1	15.6	5.2	0.0	6.5	0.0	0.0	0.0	1.3	0.0	0.0	7.8
Denmark	6.7	1.8	1.8	20.1	6.7	13.4	16.5	10.4	2.4	0.0	6.7	0.6	2.4	0.6	0.0	0.0	0.0	9.9
Finland	0.0	6.0	0.0	18.4	6.0	21.5	7.6	17.4	7.3	0.0	8.5	0.3	0.9	0.0	0.0	0.0	0.0	6.1
Trimmed mean	3.1	3.7	1.1	17.6	6.6	20.7	8.7	15.7	6.5	0.0	5.4	0.3	1.3	0.3	0.0	0.0	0.0	7.6
CTMP	3.1	3.7	1.1	17.9	6.7	21.0	8.8	16.0	6.6	0.0	5.5	0.3	1.3	0.3	0.0	0.0	0.0	7.7
Developing																		
Mexico	0.8	0.8	0.8	17.5	6.7	9.2	2.5	14.2	20.8	2.5	0.8	0.8	5.0	1.7	0.0	0.0	0.0	15.8
Brazil	6.4	2.6	10.3	18.1	5.1	10.7	10.5	8.0	5.4	1.9	1.9	1.6	2.5	0.3	0.0	0.0	0.0	14.7
Uruguay	6.3	2.1	14.6	4.2	10.5	39.6	0.0	0.0	2.1	0.0	4.2	0.0	2.1	2.1	0.0	0.0	0.0	12.2
The Gambia	10.2	0.0	8.5	15.3	5.1	32.2	1.7	5.1	0.0	0.0	0.0	8.5	1.7	0.0	1.7	0.0	6.8	3.2
Egypt	31.4	2.3	4.7	8.1	9.3	7.0	3.5	2.3	1.2	2.3	3.5	5.8	0.0	0.0	0.0	2.3	4.7	11.6
Pakistan	0.6	0.0	4.2	10.7	6.5	1.2	2.4	38.7	4.2	0.0	0.6	0.0	3.6	7.1	0.0	0.0	0.0	20.2
PNG	2.6	0.7	10.6	6.6	2.0	6.6	0.7	7.3	7.3	7.3	13.2	2.6	0.7	2.0	0.7	6.0	6.0	17.1
Rwanda	22.3	0.0	14.6	10.0	2.3	14.6	3.1	3.8	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	31.6
(adjusted)					0.75				0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	(24.1)
Trimmed mean	6.4	0.9	8.5	11.0	5.9	10.4	2.4	6.1	3.2	1.2	1.7	1.4	1.8	1.2	0.2	0.2	1.4	15.0
CTMP	8.1	1.1	10.8	14.0	7.4	13.2	3.1	7.7	4.1	1.6	2.2	1.8	2.2	2.5	0.2	0.2	1.7	29.0
Intermediate																		
South Africa	10.5	3.5	1.7	28.0	1.8	19.2	3.9	13.0	3.2	1.1	2.8	1.1	4.5	0.0	0.2	0.0	0.0	5.5
Israel	13.4	2.7	16.5	10.7	6.3	14.7	6.7	9.4	3.6	0.0	5.4	3.1	0.9	1.3	0.0	0.4	0.0	4.9
Australia	4.6	9.1	0.5	10.5	6.4	22.4	11.9	10.0	7.8	0.0	2.3	1.4	0.9	0.5	0.0	0.0	0.0	11.7
Trimmed mean	10.0	4.3	4.0	13.6	5.6	19.0	7.1	10.4	4.2	0.2	3.2	1.6	1.5	0.6	0.0	0.1	0.0	6.4
CTMP	10.9	4.7	4.4	14.8	6.1	20.7	7.7	11.3	4.6	0.2	3.4	1.7	1.6	0.6	0.0	0.1	0.0	7.0

oping countries are, in descending order, 14, 6, 1, 5, 19, 9, 23, 18, 15 and 7.

Serotype 14 and serogroups 6 and 19 are consistently among the most frequent sterile site isolates from sick children regardless of country. Among the five developed countries, serotype 14 and groups 6 and 19 have CTMPs of 22.0, 17.9 and 16.0, respectively. Among the eight developing countries, serotype 14 and groups 6 and 19 have CTMPs of 13.2, 14.0 and 7.7%, respectively.

Serotypes 1 and 5 rank 4th and 3rd among the developing countries, with CTMPs of 8.1 and 10.8%, respectively. Among developed countries, however, serotypes 1 and 5 rank 9th and 11th with CTMPs of 3.1 and 1.1%, respectively.

Serogroup 18 is isolated more frequently in developed then in developing countries, ranking 4th with a CTMP of 8.8%. In developing countries it ranks 8th with a CTMP of 3.2%.

Serotype 4, which is included in the proposed heptavalent vaccine Formula A, is not one of the seven serotypes or groups most commonly isolated from children in either developed or developing countries. It has a CTMP of 3.7% and 1.1% and ranks 8th and 14th in developed and developing countries, respectively.

A wider range of serotypes or groups cause a substantially greater proportion of disease among children in developing compared with developed countries. In developed countries the leading 10 serotypes or groups comprise 72.8% of all isolates, whereas in developing countries the leading 10 serotypes or groups comprise 74.9% of all isolates. In addition the prevalence of some serotypes or groups varies widely between developing countries. For example serotype 46 is commonly isolated in The Gambia (6.8%, Rank 5), PNG (6.0%, Rank 8) and Egypt (4.7%, Rank 5) but is rarely isolated in other developing countries.

Serotype and group prevalence by age group and specimen type. In most studies in which age-stratified data were available (the United States, Belgium, Israel, PNG and South Africa), serotype or group prevalence did not differ for children <2 years *vs.* children 2 to 4 years old. In Finland, however, serotype 14 infections were identified more often in children <2 than in children 2 to 15 years old.[19]

In two of six studies reporting serotype or group prevalence by specimen type, prevalence differed significantly for blood *vs.* CSF isolates. In the United States serotypes 4 (231/3336 (6.9%) *vs.* 6/324 (1.9%), RR = 3.7, ($P < 0.001$) and 11 (925/3336 (27.7%) *vs.* 72/324 (22.2%), RR = 1.3, ($P = 0.04$) and serogroup 9 (247/3336 (7.4%) *vs.* 13/324 (4.0%), RR = 1.9, ($P = 0.03$) were significantly more likely to be isolated from blood than from CSF. Serogroups 6 (85/324) (26.2%) *vs.* 555/3336 (16.6%), RR = 1.6, ($P < 0.001$) and 7 (12/324 (3.7%) *vs.* 49/3336 (1.5%), RR = 2.5, $P = 0.006$ were more likely to be isolated from CSF. In PNG serogroup 19 (10/56 (17.9%) *vs.* 1/95 (1.1%), RR = 17.0, $P = 0.001$) and serotype 14 (7/56 (12.5%) *vs.* 3/95 (3.2%), RR = 4.0, $P = 0.04$) were isolated more frequently from blood than from CSF, whereas serotypes 2 (10/95 (10.5%) *vs.* 1/56 (1.8%), RR = 5.9, $P = 0.055$ and 5 (14/95 (14.7%) *vs.* 2/56 (3.6%), RR = 4.1, $P = 0.06$) were more likely to be isolated from CSF.

Serotype or group prevalence over time. Among the two studies reporting annual serotype or group prevalence, overall distribution varied significantly by year for South Africa ($P = 0.03$) but not for the United States ($P = 0.18$). Blood and CSF specimens collected from children <5 years old at several sites throughout South Africa from 1987 to 1991 showed significant variation in serotype or group distribution in 1987 ($P = 0.02$) and in 1991 ($P = 0.05$) compared with other years. Serogroup 23 was the fifth most frequently isolated serotype or group in 1989 and 1990 but ranked 12th in 1991. Similarly serogroup 18 ranked fifth in 1987 and 1988 but was not among the top seven serotypes or groups from 1989 through 1991.

Variation in serogroup coverage over time. Temporal variation in serotype or group prevalence in South Africa resulted in variation of serogroup coverage over a 5-year period for Formula A between 69.1 and 75.5%; Formula B coverage varied between 76.5 and 83.2%. No annual differences in coverage were statistically significant.

Serogroup coverage of potential vaccine formulas by country group. Table 3 lists the 8 vaccine formulas for which serogroup coverage was determined. Table 4 lists the serogroup coverage for each of the 8 formulas by country group. In developed countries serogroup coverage for Formula A is greater than that for Formula B (80.7% *vs.* 74.5%). Formula A coverage by country ranges from 71 to 89% (Table 5) and is significantly greater than that of Formula B in 2 of 5 countries (the United States and Finland). In developing countries Formula B serogroup coverage is greater than that of Formula A (60.9% *vs.* 50.6%). Formula B coverage by country ranges from 42 to 73% and is significantly greater than that of Formula A in 4 of 8 countries (Brazil, Rwanda, Egypt and PNG).

The Developed Country Custom 7 vaccine (which includes the seven most common serotypes or groups from developed countries) provides slightly better serogroup coverage than Formula A (82.5% *vs.* 80.7%) for the developed country group. The Developed Country Custom 9 vaccine increases coverage to 89.3% and gives significantly better coverage than Formula A in each of the 5 countries.

The Developing Country Custom 7 vaccine increases serogroup coverage slightly compared with Formula B for the developing country group (65.3% *vs.* 60.9%). The Developing Country Custom 9 vaccine increases coverage to 70.6% and provides significantly better coverage than Formula B in 5 of the 8 countries (Mexico, Brazil, Uruguay, Egypt and Pakistan).

Among the four nanovalent formulas the Developed and Developing Custom 9 formulas by definition provide the best coverage for their respective country groups. However, serogroup coverage of the Global 9 formula approximates that of the Developed Country Custom 9 vaccine (86.7% *vs.* 89.3%) and equals that of the Developing Country Custom 9 vaccine (70.6%) for developed and developing country groups. Formula A + B vaccine, which combines all serotypes of Formulas A and B (1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F), provides the lowest coverage for developed and developing country groups (85.0 and 69.5%, respectively) among the four nanovalent formulas.

Serogroup coverage *vs.* true vaccine coverage. Serotype-specific data were available from seven countries (United States, Mexico, Brazil, Uruguay, Denmark, Egypt and Pakistan). Serogroup coverage exceeded serotype-related coverage for Formula A by a median of 9.1% (interquartile range, 6.2 to 12.8%) and for Formula B by a median of 4.8% (interquartile range, 2.1 to 10.0%).

TABLE 3. Serotype antigens included in proposed and potential heptavalent and nanovalent pneumococcal conjugate vaccine formulations

Vaccine	Serotype Antigens										
Formula A		4		6B		9V	14		18C	19F	23F
Formula B	1		5	6B			14		18C	19F	23F
Formula A + B	1	4	5	6B		9V	14		18C	19F	23F
Developed Country Custom 7				6B	7F	9V	14		18C	19F	23F
Developed Country Custom 9	1	4		6B	7F	9V	14		18C	19F	23F
Developing Country Custom 7	1		5	6B		9V	14			19F	23F
Developing Country Custom 9	1		5	6B		9V	14	15B	18C	19F	23F
Global 9	1		5	6B	7F	9V	14		18C	19F	23F

TABLE 4. Serogroup coverage of proposed and potential pneumococcal conjugate vaccine formulas, by country group

	Serotype Coverage (%)					
	Formula A	Formula B	Custom 7	Formula A + B	Global 9	Custom 9
Developed countries	80.7	74.5	82.5	85.0	86.7	89.3
Developing countries	52.2	60.9	65.3	69.5	70.6	72.6

TABLE 5. Serogroup coverage for proposed pneumococcal conjugate vaccine formulas A and B, by country

Country	*N*	Formula A	Formula B	*P*
Developed				
United States	3523	88.9	76.8	< 0.001
Spain	167	64.4	67.2	0.46
Belgium	77	77.9	72.8	0.43
Denmark	164	71.3	71.3	0.93
Finland	235	84.2	72.2	< 0.001
Developing				
Mexico	120	71.7	65.8	0.06
Brazil	308	60.4	69.4	0.002
Uruguay	48	58.5	66.8	0.45
Rwanda	130	33.0	68.4	< 0.001
The Gambia	59	59.4	73.0	0.06
Egypt	86	33.7	58.2	0.002
Pakistan	168	63.7	62.0	0.50
Papua New Guinea	151	31.2	41.7	0.002
Intermediate				
South Africa	1138	72.6	79.5	< 0.001
Israel	224	54.1	75.0	< 0.001
Australia	219	78.1	67.1	< 0.001

DISCUSSION

This review reveals important limitations in available serotype and group data from sterile site isolates in children. Data that are available from only a small number of countries may not be representative of all children in the developed or developing world. For example data from India and China, countries that include the majority of the world's children, were not available for our analysis. Also particular study methods make generalizability of serotype and group data difficult: (1) the small sample size of many studies limits the precision of serotype or group prevalence and vaccine coverage estimates; (2) studies of short duration may not accurately portray serotype or group prevalence because of annual fluctuations in serotype-specific infection; (3) obtaining isolates from children who are brought to one or several study hospitals is likely to result in a greater degree of concordance of serotypes or groups than actually exists nationwide because children from the same cachement area are likely to have been exposed to the same pneumococcal strains; finally (4) if serotype or group distribution is different for lung and blood *vs.* CSF isolates, vaccine coverage estimates to prevent invasive disease secondary to pneumonia, which is more common than meningitis, may be inaccurate when isolates from CSF have been included in determining serotype or group prevalence.

The limitations and variation of study methods preclude statistical comparisons of serotype and group prevalence between countries or regions. Comparative analysis of results of prospective seroprevalence studies would be facilitated by the use of similar enrollment criteria (i.e. including only children < 5 years old who have not received anti-pneumococcal antibiotics and who have pneumococcal isolates from lung tissue, pleural fluid, blood and/or CSF) and by collection of a sufficient number of isolates from representative populations to provide adequate precision in serotype and group prevalence estimates. Potential biases introduced by temporal variation could be reduced by collecting isolates during 3 to 5 consecutive years. Apparent differences in serogroup prevalence by country and region could then be systematically evaluated to guide more confidently vaccine design and strategy.

Despite these limitations our analysis has clarified certain issues concerning the design and use of vaccines to reduce the burden of pneumococcal disease among children in developed and developing countries: serotype 14 and serogroups 6 and 19 predominate worldwide; serotypes 1 and 5 are common in most developing countries; and serogroup 18 is common in developed but not in developing countries.

Data from developing countries indicate that many serotypes or groups that do not frequently cause disease in children from developed countries are frequently but inconsistently isolated from children in developing countries. This difference may reflect increased susceptibility of children from developing countries to a greater variety of pneumococcal strains because of malnutrition, coincident diseases (e.g. malaria) and indoor smoke. Also household crowding and lack of personal hygiene (i.e. hand-washing) among numerous baby and child caregivers may facilitate greater transmission of respiratory pathogens in developing as opposed to developed countries.

The greater number of serotypes and groups causing disease in developing countries implies that optimal coverage for individual countries would be obtained by customizing vaccine formulas for national use according to national serotype and group data. However, such a vaccine strategy would be expensive, requiring national pneumococcal surveillance for several consecutive years to determine which serotypes to include in a nationally designed vaccine formula. Production of a standardized vaccine based on the leading serotypes and groups causing disease globally would likely be a less expensive option. A single nanovalent formula including serotypes 1, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F may provide the greatest vaccine coverage in preventing life-threatening pneumococcal infections in children worldwide.

It is important to note, however, that no single vaccine formula of limited valency will provide comprehensive coverage for children in all developing countries. The variety of serotypes and groups causing disease among children from developing countries result in wide variations of vaccine coverage even with a customized nanovalent formulation. Although the Developing Country Custom 9 formula by definition provides the best coverage of all potential vaccine candidates evaluated in this study for developing countries,

individual developing country serogroup coverage for this formula ranges from 44 to 90%. Increasing the number of serotypes included in a customized formula beyond nine might benefit individual countries in a particular year. However, such an increase cannot substantially improve coverage overall because incremental gains in coverage decrease with each successive serotype added to the vaccine.

Factors other than serotype or group coverage, such as immunogenicity (or a different immunologic correlate of protection) and clinical efficacy, are important determinants of the effectiveness of proposed pneumococcal conjugate vaccines to reduce the morbidity and mortality from pneumococcal disease. Most Phase II (immunogenicity) studies that have been published have generally included a small number of vaccine serotypes.[27–29] More importantly because antibody concentrations corresponding to protection are not known, the potential impact of possible conjugate vaccine formulas cannot be determined until Phase III (efficacy) study results are known.

Future hopes of reducing childhood mortality by vaccinating against pneumococcus do not lie solely in the pneumococcal conjugate vaccine formulas mentioned here.[30] Although global use of a conjugate vaccine may reduce the high rates of childhood mortality in developing countries, the geographic and temporal variation of pneumococcal strains isolated from sick children suggests that a species-wide, protein-based vaccine may be needed to provide more widespread protection against death and disease caused by pneumococcus. One such vaccine might conjugate pneumococcal capsular polysaccharides to an immunogenic pneumococcal protein. Additional research concerning such proteins, including pneumolysin toxoid, pneumococcal surface protein A (Psp-A) and a 37-kDa protein unique to *S. pneumoniae*,[31–33] may be the key to developing a vaccine that provides optimal protection against pneumococcal disease in children worldwide.

ACKNOWLEDGMENTS

This publication is part of a series of reviews of interventions to prevent childhood pneumonia, commissioned by the WHO Programme for the Control of Acute Respiratory Infections in association with the Maternal and Child Epidemiology Unit of the London School of Hygiene and Tropical Medicine, with the support of the U.K. Overseas Development Association, World Health Organization and UNICEF. The reviews were coordinated by Julian Lob-Levyt, Paul Arthur and Betty Kirkwood at the London School of Hygiene and Tropical Medicine and Tropical Medicine and by Sandy Gove at WHO Programme for the Control of Acute Respiratory Infections.

REFERENCES

1. Shann F. Etiology of severe pneumonia in children in developing countries. Pediatr Infect Dis J 1986;5:247–52.
2. Barker J, Gratten M, Riley I, et al. Pneumonia in children in the Eastern Highlands of Papua New Guinea: a bacteriologic study of patients selected by standard clinical criteria. J Infect Dis 1989;159:348–52.
3. Forgie IM, O'Neill KP, Lloyd-Evans N, et al. Etiology of acute lower respiratory tract infections in Gambian children: I. Acute lower respiratory tract infection in infants presenting at the hospital. Pediatr Infect Dis J 1991;10:33–41.
4. Forgie IM, O'Neill KP, Lloyd-Evans N, et al. Etiology of acute lower respiratory tract infections in Gambian children: II. Acute lower respiratory tract infection in children ages one to nine years presenting at the hospital. Pediatr Infect Dis J 1991;10:42–7.
5. Weissenbacher M, Carballal G, Avila M, et al. Etiologic and clinical evaluation of acute lower respiratory tract infections in young Argentinian children: an overview. Rev Infect Dis 1990;12(Suppl 8):S889–98.?
6. Leowski J. Mortality from acute respiratory infection in children less than 5 years of age: global estimates. World Health Stat Q 1986;39:138–44.
7. Garenne M, Ronsmans C, Campbell H. The magnitude of mortality from acute respiratory infections in children under 5 years in developing countries. World Health Stat Q 1992;46: 180–191.
8. Sazawal S, Black RE. Meta-analysis of intervention trials on case management of pneumonia in community settings. Lancet 1992;340:528–33.
9. Applebaum PC. World-wide development of antibiotic resistance in pneumococci. Eur J Clin Microbiol 1987;6:367–77.
10. Klugman KP. Pneumococcal resistance to antibiotics. Clin Microbiol Rev 1990;3:171–96.
11. Robbins JB, Austrian R, Lee CJ, et al. Considerations for formulating the second generation pneumococcal capsular polysaccharide vaccine with emphasis on cross-reactive types within groups. J Infect Dis 1983;148:1136–59.
12. Douglas RM, Paton JC, Duncan SJ, Hansman DJ. Antibody response to pneumococcal vaccination in children younger than five years of age. J Infect Dis 1983;148:131–7.
13. Witt CS, Pomat W, Lehmann D, Alpers MP. Antibodies to pneumococcal polysaccharides in pneumonia and response to pneumococcal vaccination in young children in Papua New Guinea. Clin Exp Immunol 1991;83:219–24.
14. Rijkers GT, Dollekamp EG, Zegers BJM. The *in vitro* B-cell response to pneumococcal polysaccharides in adults and neonates. Scand J Immunol 1987;25:447–52.
15. Timens W, Boes A, Rozeboom-Uiterwijk T, Poppema S. Immaturity of the human splenic marginal zone in infancy. J Immunol 1989;143:3200–6.
16. Taunay AE, Austria R, Landgraf IM, Vieira MFP, Melles CEA. Sorotipos de *Streptococcus pneumoniae* isolados de líquido cefalorraquidiano no período de 1977–1988 na cidade de Sao Paulo, Brasil. Rev Inst Med Trop Sao Paulo 1990;32:11–5.
17. Mogdasy MC, Camou T, Fajardo C, Hortal M. Colonizing and invasive strains of *Streptococcus pneumoniae* in Uruguayan children: type distribution and patterns of antibiotic resistance. Pediatr Infect Dis J 1992;11:648–52.
18. Fenoll A, Bourgon CM, Muñóz R, Vicioso D, Casal J. Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolates causing systemic infections in Spain, 1979–1989. Rev Infect Dis 1991;13:56–60.
19. Eskola J, Takala AK, Kela E, Pekkanen E, Kalliokoski R, Leinonen M. Epidemiology of invasive pneumococcal infections in children in Finland. JAMA 1992;268:3323–7.
20. Guirguis NI, Helmy MF, Mohamed MR, Ali RH. A suggested vaccine formulation for the control of pneumococcal meningitis in Egypt. J Egypt Public Health Assoc 1990;65:291–303.
21. Bogaerts J, Lepage P, Taelman H, et al. Antimicrobial susceptibility and serotype distribution of *Streptococcus pneumoniae* from Rwanda, 1984–1990. J Infect 1993;27:157–68.
22. Mastro TD, Ghafoor A, Nomani NK, et al. Antimicrobial resistance of pneumococci in children with acute lower respiratory tract infection in Pakistan. Lancet 1991;1:156–9.
23. Mastro TD, Nomani NK, Ishaq Z, et al. Use of nasopharyngeal isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae* from children in Pakistan for surveillance of antimicrobial resistance. Pediatr Infect Dis J 1993;12:824–30.
24. Hansman D. Serotypes in pneumococcal disease: a ten year study in Australia 1970 through 1979. Aust NZ J Med

1983;13:359–64.
25. Gratten M, Montgomery J. The bacteriology of acute pneumonia and meningitis in children in Papua New Guinea: assumptions, facts and technical strategies. P N G Med J 1991;34:185–98.
26. Gratten M, Barker J, Shann F, et al. The aetiology of purulent meningitis in highland children: a bacteriological study. P N G Med J 1985;28:233–40.
27. Steinhoff MC, Edwards K, Keyserling H, Johnson C, Madore D, Hogerman D. Immunogenicity and safety of 3 bivalent *S. pneumoniae* conjugate vaccines in young children [Abstract 1284]. Presented at the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, CA, October, 1992. Washington, DC: American Society for Microbiology, 1992.
28. Vella PP, Marburg S, Staub JM, et al. Immunogenicity of conjugate vaccines of pneumococcal capsular polysaccharide types 6B, 14, 19F, and 23F with meningococcal outer membrane protein complex. Infect Immun 1992;60:4977–83.
29. Nieminen T, Virolainen A, Käyhty H, Leinonen M, Eskola J. Immune response to tetravalent pneumococcal conjugate vaccine in adults [Abstract 1283]. Presented at the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, CA, October, 1992. Washington, DC: American Society for Microbiology, 1992.
30. Siber GR. Pneumococcal disease: prospects for a new generation of vaccines. Science 1994;265:1385–7.
31. Paton JC, Lock RA, Lee C, et al. Purification and immunogenicity of genetically obtained pneumolysin toxoids and their conjugation to *Streptococcus pneumoniae* type 19F polysaccharide. Infect Immun 1991;59:2297–304.
32. McDaniel LS, Sheffield JS, Delucchi P, Briles DE. PspA, a surface protein of *Streptococcus pneumoniae*, is capable of eliciting protection against pneumococci of more than one capsular type. Infect Immun 1991;59:222–8.
33. Talkington DF, Koenig A, Russell H. The 37-kDa protein of *Streptococcus pneumoniae* protects mice against fatal challenge [Abstract E-29]. Presented at the 92nd General Meeting of the American Society for Microbiology. Washington, DC: American Society for Microbiology, 1992.

Pediatr Infect Dis J, 1995;14:510–16
0891-3668/95/$03.00/0

Vol. 14, No. 6
Printed in U.S.A.

Comparison of 10% povidone-iodine and 0.5% chlorhexidine gluconate for the prevention of peripheral intravenous catheter colonization in neonates: a prospective trial

JEFFERY S. GARLAND, MD, SM,[1] ROSANNE K. BUCK, MSN, CNNP, PATRICIA MALONEY, MSN, DEBORAH M. DURKIN, BSN, SUZANNE TOTH-LLOYD, MSN, MARYBETH DUFFY, MSN, CNNP, PAULINE SZOCIK, BSN, TIMOTHY L. MCAULIFFE, PHD AND DONALD GOLDMANN, MD

The purpose of the study was to compare the efficacy of 10% povidone-iodine with that of 0.5% chlorhexidine gluconate in 70% isopropyl alcohol for the prevention of peripheral intravenous catheter colonization in neonates. This was a multicenter, nonrandomized prospective study in a tertiary neonatal intensive care setting in which povidone-iodine and chlorhexidine gluconate were each used as antiseptic skin preparations over sequential 6-month periods. During the first 6 months of the study when povidone-iodine was in use 9.3% (38 of 408) of catheters were colonized. During the second 6 months of the study when chlorhexidine gluconate was in use, catheter colonization occurred in 4.7% (20 of 418, $P = 0.01$). Catheter-related bacteremia occurred during only 0.2% (2 of 826) of all catheterizations. Heavy skin colonization before catheter insertion (relative risk, 3.6; 95% confidence interval, 1.9, 7.0), catheterization ≥72 hours (relative risk. 2.0; 95% confidence interval, 1.01, 3.8) and gestational age ≤32 weeks (relative risk, 1.8; 95% confidence interval, 1.02, 3.3) increased coloniza-

Accepted for publication March 16, 1995.
From the Joint Program in Neonatology, Harvard Medical School (JSG), Children's Hospital (RKB, PM, DMD, STL, MD, PS), and the Division of Infectious Diseases and Hospital Epidemiology Program, Children's Hospital and Department of Pediatrics, Harvard Medical School (DG), Boston, MA, and the Department of Biostatistics, Medical College of Wisconsin, Milwaukee, WI (TLM).
[1] Current address: St. Joseph's Hospital, Milwaukee, WI.
Presented in part at the annual meeting of the Society of Pediatric Research, May 4, 1994, Seattle, WA.
Key words: Neonate, intravenous therapy, catheter colonization, cutaneous antisepsis.
Address for reprints: Jeffery S. Garland, M.D., S.M., 5000 West Chambers Street, Milwaukee, WI 53210.