

1 Ten-year surveillance of pneumococcal infections in Temuco, Chile.  
2 Implications for vaccination strategies.

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**Running title:** Ten-year surveillance of pneumococcal infections in Temuco, Chile.

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1 **ABSTRACT**

2 We monitored *Streptococcus pneumoniae* serotypes causing invasive infections in patients admitted to  
3 one hospital in southern Chile during a 10-year period (1994 - 2004). All specimens isolated from  
4 patients with invasive *S. pneumoniae* infections were serotyped at the CDC in Atlanta. A total of 508  
5 isolates belonged to 58 serotypes. There were 95 infections in the <2 year-old age group, 33 infections  
6 in the 2-4 age group, 61 infections in the 5-14 age group, 66 infections in the 15-44 age group, 134  
7 infections in the 45-64 age group, and 120 infection  $\geq 65$  age group. The ten serotypes isolated with the  
8 highest frequency in all groups were, in decreasing order, 1, 3, 14, 5, 19F, 6B, 7F, 12F, 23F, and 6A.  
9 The 10 most frequent isolates in children under two years of age were 1, 6B, 14, 19F, 5, 23F, 6A, 9V,  
10 and 7F. In patients  $\geq 65$  years, the most common serotypes were 3, 7F, 1, 14, 19A, 23F, 19F, 35B, 4,  
11 and 5. Penicillin resistance was detected in 14 (2.7 %) clinical isolates since 1998, with 13 resistant  
12 strains identified since 2001. Vaccine coverage for the 7-valent conjugate vaccine was 42% for children  
13 <2 years of age. This study is important for the design of vaccines for this region and to evaluate public  
14 health measures to decrease pneumococcal infections.

15  
16 **INTRODUCTION**

17 *Streptococcus pneumoniae* infections are caused by 90 serotypes grouped in 46 serogroups based on  
18 immunological similarities (13). The capsular serotypes of *S. pneumoniae* causing invasive infections  
19 vary according to the geographic location and socioeconomic status of a study population (1, 2, 14, 32,  
20 33). Few studies have monitored serotype changes in invasive pneumococci over time, especially in the  
21 absence of increased antibiotic resistance, vaccine selective pressure, socioeconomic changes, or  
22 debilitating diseases.

23  
24 In a previous communication, we reported that age was clearly a factor in the overall incidence of  
25 invasive infections, with infections being most frequent in the first years of life (15). Selective pressure

1 has driven the emergence of worldwide antibiotic resistance of some serotypes (1, 2, 7, 17, 33).  
2 Immunization practices and antibiotic resistance due to preventive antibiotic use in special-risk  
3 populations are important factors influencing the incidence of serotypes causing infection (29). Host-  
4 related factors also contribute to susceptibility to pneumococcal infection. Underlying heart and central  
5 nervous system diseases, as well as malignancies, are frequently identified in patients developing  
6 invasive infections (17) as are underlying immune abnormalities like HIV infection which are major risk  
7 factors for invasive pneumococcal infections (23).

8  
9 We have monitored *S. pneumoniae* serotypes associated with invasive and sterile-site infections in  
10 patients admitted to one regional general hospital in Southern Chile during a 10-year period. During this  
11 study period, the patient population remained relatively homogenous and without HIV infection.  
12 Pneumococcal immunization programs have not been implemented for any age group. Our results  
13 document that even in the absence of known selective pressures changes in pneumococcal disease  
14 incidence and serotype distributions associated with different age groups.

15

## MATERIALS AND METHODS

**Study population.** The study population consisted of patients of all ages seeking medical care and being admitted to any of the inpatient services of the Hospital Regional in Temuco (Hospital Dr. Hernán Henríquez A) in southern Chile. The lower and middle income populations of this city generally seek medical care from the Chilean National Health Service at this hospital where patients are admitted to the Internal Medicine, Surgery, Obstetrics and Pediatric services. All samples are sent to the Central Laboratory of the hospital.

All patients admitted to the hospital are screened for both HIV-1 and HIV-2 serology by ELISA (Abbott Laboratories, Chicago, IL). All patients with pneumococcal infections in this study were HIV seronegative.

Bacterial cultures were obtained following the same criteria during the entire observation periods. According to Emergency Service guidelines, cultures are obtained only in patients whose clinical presentation is severe enough to warrant an in-hospital observation period. Blood cultures are obtained in febrile patients with systemic symptoms. Spinal fluid was cultured in patients with clinical suspicion of meningitis or central nervous system compromise. According to protocol, no outpatients are evaluated with cultures.

**Sample definition and collection.** All *S. pneumoniae* strains from invasive infections (IPD) were included in this study. These included strains isolated from blood, spinal fluid, pleural fluid, or ascites. Strains isolated from sputum or mucosal sites such as the conjunctiva, middle ear, or sinus cavities were not included in this study.

1 The same laboratory personnel performed all cultures and *S pneumoniae* identification over the 10 year  
2 study period. Samples were collected around the clock and the laboratory was staffed at all times. From  
3 1994 to 2002 an in-house made culture media was used (heart-brain broth). (5)

4  
5 In 2002 the automated Bac-Alert heart brain broth (BioMerieux, Lyon, France) was introduced and has  
6 been used since then. Clinical isolates were collected between February 1994 and November 2004. The  
7 analysis of serotypes was performed for the entire observation period and also for each of 5 two year  
8 periods: 94-96 (this period included some serotypes isolated in 2004); 97-98; 99-00; 01-02; 03-04.  
9 Results for the first 5 years of surveillance have been previously published (15).

10  
11 **Pneumococcal serotyping.** Pneumococcal serotyping was performed in the pneumococcal serotyping  
12 laboratory at the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia. Before  
13 serotyping, cultures were transferred to 5% sheep blood agar plates (Difco Laboratories, Detroit,  
14 Michigan) overnight. All serotyping results were confirmed by the Quellung typing with absorbed  
15 polyclonal rabbit sera.

16  
17 **Antibiotic sensitivity** of all isolates was determined by the E-test for penicillin. Penicillin-resistant  
18 isolates were also tested for cefotaxime, ceftriaxone, and vancomycin (13, 16). For analysis, the study  
19 population was divided into three age groups: under five years of age, 5 to 64 years of age, and over 64  
20 years of age.

## 22 RESULTS

### 23 Bacterial culture results

24 An exact account of all blood and sterile fluid cultures performed was kept for the last five years of the  
25 observation period. There was no significant change in the percentages of positive cultures over this

1 period of time. The yearly average number of blood cultures was **6604 (5023-7185)** and of sterile fluids it  
2 was **1230 (1513- 1031)**. The average percentage of cultures positive for bacteria was **11.6% (9.8 to 14.6)**  
3 for blood cultures and **2.7% (2.4 - 3.1) %** for sterile fluid cultures. The percentage of cultures positive for  
4 *S. pneumoniae* was **1.14 (08 to 1.47)** for blood cultures and **1.1 (0.9 – 1.5)** for sterile fluid cultures.

5  
6 **Epidemiology.** The total population cared for at the Temuco Regional Hospital during the 10-year  
7 study period in each of these age groups remained stable. The average yearly population in different age  
8 groups was as follows: < 2 years, 11,311 (10,969 – 11,671) with a yearly incidence of 80.0 IPD  
9 /100,000; children 0-5 y (Including the previous group <2years) 28,820 children (range 27,454-29,738)  
10 with a yearly incidence of IPD of 46.7/100,000; the yearly average population of 5 to 64 year olds was  
11 250,621 individuals (range 213,823-278,471) with a yearly incidence of 9.95/100,000. The average  
12 yearly population  $\geq$  65 years was 19,050 (range: 15,780-21,911) with an average yearly incidence of  
13 60.0 /100,000.

14  
15 **Serotypes isolated over ten years.** The total number of isolates from all age groups was 514. Only  
16 five were not typeable and were not included in this report. Five hundred and nine *S. pneumoniae*  
17 isolates representing 58 serotypes were isolated during the entire study period (**Table 1**). Of the 58  
18 serotypes, 14 were observed only once and five additional serotypes only twice. Altogether, 27  
19 serotypes were observed less than five times. The highest number of infections was observed in  
20 children under 2 years of age (n=95) and in patients  $\geq$  45 years old (254 IPD). The ten serotypes  
21 identified with the highest frequency were, in decreasing order: 1, 3, 14, 5, 19F, 6B, 7F, 12F, 23F, and  
22 6A.

1 **Serotypes and age.** The overall distribution of serotypes causing infection in the six different age  
2 groups is shown in Table 1. Some serotypes were isolated exclusively in children < 2 or in patients  $\geq 65$   
3 years. The most commonly isolated serotypes in children <2 years are serotypes 1, 6B, 14, 19F and 5;  
4 serotypes 3, 7F, 4 and 18C were never isolated from this age group. In children 2-4 years of age the  
5 most frequent serotype is again serotype 1, followed by 23F. Again, no serotype 3 and 7F were isolated.  
6 Serotype 3 and 7F appears in patients 5 years and older. In patients  $\geq 65$  years, serotypes 3, 7F become  
7 the most frequently isolated serotypes followed by 1 and 14. Serotype 5 and 6B were isolated in only  
8 three patients each in this age group.

9  
10 The serotypes identified most frequently in each age group tend to be isolated in each of the five two-  
11 year periods. For children under 2 years the most frequent serotypes isolated throughout the study were  
12 1, 6B, 14 and 19F. In contrast, for patients  $\geq 65$  years, they were serotypes 3, 7F and 1. All other  
13 serotypes were isolated in only some of the two-year periods. Notably, serotype 5 was isolated in  
14 children <2 years of age six times in 1997-98, but only two additional times in the remaining  
15 observation period. In patients  $\geq 65$  years old, serotype 14 was not identified in the first 4 years of the  
16 study, but was isolated regularly starting in 1999. Sporadic isolation of some serotypes is also frequent  
17 in each age group.

18

19 **Antibiotic resistance.**

20 Antibiotic resistance was identified in only one clinical isolate in 1988. This serotype 23F strain was  
21 isolated from a child younger than five years of age. It was highly resistant to penicillin and cefotaxime,  
22 but not to vancomycin (8). Thirteen additional resistant serotypes were isolated starting in 2001. The  
23 resistant strains included serotype 14 (4 isolates) serotype 11A (2 isolates) and serotypes 5, 6B, 9V 18F,  
24 19A, 19F and 23F. All strains were sensitive to cefotaxime, ceftriaxone, and vancomycin. Notably, two

1 penicillin resistant 11A isolates were isolated in two consecutive years. Since detection of antibiotic  
2 resistance in 2001, the incidence of resistance has remained constant.

3

#### 4 **Vaccine coverage.**

5 The estimated vaccine coverage offered by different vaccines to patients of different age groups in the  
6 five two-year periods of this study is summarized in **Table 2**. Overall, the coverage offered by the  
7 different vaccines for each age group remained stable over the entire observation period. The 7-valent  
8 conjugate vaccine coverage for children <2 years of age ranged from 40-60%, with much lower  
9 coverage in all other age groups. Of 23 serotypes in the polysaccharide vaccine, one (serotype 2) was  
10 never isolated. All other vaccine serotypes were isolated on at least five occasions with 67, 36 and 34  
11 isolates recovered for serotypes 1, 3 and 14, respectively. However, coverage by the 23-valent vaccine  
12 was only 61-68% for patients  $\geq 65$  years of age.

## DISCUSSION

### **Epidemiology.**

The incidence of pneumococcal infection varies widely in the world and even varies within countries (20). The incidence of invasive pneumococcal disease is influenced by age, immunization status, and ethnic background (12). Our results further confirm the high incidence of pneumococcal infections in young children that has been observed in other studies (6, 31). This observation suggests that there should be a continuous program of monitoring invasive pneumococcal infections.

Recently, HIV infection has been identified as an important risk factor for invasive pneumococcal disease (23). This factor was ruled out for our population because there were no HIV-positive individuals in the survey

**Pneumococcal serotypes causing infection over a 10-year period.** Of the 58 serotypes found among individuals over ten years, 27 serotypes were found less than five times suggesting that some serotypes are rarely associated with invasive infection even when present in a community. Bacterial factors are likely to influence the serotype spectrum that is associated with invasive infections. When both nasopharyngeal carriage and invasive infection isolates have been studied from the same individual, a high degree of correlation in serotypes has been found (9). On the other hand, some pneumococcal serotypes found colonizing the nasopharynx have little tendency to cause invasive disease (14, 19, 30). These observations suggest that certain pneumococcal serotypes have characteristics that are advantageous for invasiveness.

Serotype distribution within age groups changed over the 10-year period of this survey. However, some differences among age groups remained throughout the entire study period suggesting the importance of

1 continuing to search for specific susceptibilities for some serotypes, especially in young children and the  
2 elderly.

3  
4 The absence of serotype 3 pneumococcal infections among children under five years of age was  
5 observed throughout the survey, although this serotype was a frequent cause of infection in all ages  
6 above five years of age. This observation is consistent with several studies that have shown that  
7 serotype 3 pneumococci are frequently recovered from the respiratory tract (10, 16), but are infrequent  
8 causes of invasive *S. pneumoniae* infections in children (21, 25, 27). In a study of invasive infections in  
9 children under five years of age in Santiago, Chile, serotype 3 caused only 3.3% of infections (18).

10 The literature suggests that in young children serotypes 1, 5 and 7F play a dominant role in IPD  
11 In outpatient study population only serotypes 1 and 5 were isolated in patients under 5 years of age,  
12 while serotype 7F was isolated in older age groups. (11)

13  
14 The absence of serotype 14 in isolates from elderly patients in the first part of our study was surprising  
15 (15) because this was a serotype commonly isolated from patients over 60 years of age in the United  
16 States and New Zealand (3, 21). However, serotype 14 was isolated from the elderly in the second part  
17 of our surveillance suggesting that the initial observation was not due to an intrinsic resistance of older  
18 individuals to this serotype.

19  
20 All the data presented in this study was based on Quellung typing with absorbed polyclonal rabbit sera.  
21 Serotype identity may vary if different typing methods are used like monoclonal antibody typing (**Yu**  
22 **2005; Lin 2006**). For example, using this methodology a new serotype (6C) has been identified. This  
23 serotype was not detected using the traditional typing method. (**Park 2007 JCM online**)

1 In our population there is no herd immunity since no immunization against pneumococcal infection has  
2 been introduced. Any change in serotype distribution is likely due to natural changes in the serotypes in  
3 circulation and/or the development of natural immunity in the population.

#### 5 **Antibiotic resistance**

6 During the first five years of the study, only one clinical isolate (serotype 23F) was found to be highly  
7 resistant to penicillin and cefotaxime, but not to vancomycin (8). This high level resistance was not  
8 identified in any strain during the remainder of the study. Most antibiotic resistant strains isolated since  
9 2001 in Temuco have been described to have developed antibiotic resistance worldwide (12). Serotypes  
10 commonly associated with antibiotic resistance worldwide are 6A, 6B, 9V, 14, 19A, 19F, and 23F. A  
11 higher rate of nasopharyngeal colonization and exposure to antibiotics may have contributed to the  
12 development of antibiotic resistance in these serotypes (12). The identification of two 11A isolates  
13 resistant to penicillin confirms the potential for developing penicillin resistance of this serotype  
14 observed earlier (24). All 11A isolates that developed penicillin resistance belonged to a single clone  
15 (ST156). We plan to determine if the resistant isolates identified in our study are similar to those  
16 described earlier by multilocus sequence typing.

17  
18 Interestingly, after 2001, we did not observe an increase in antibiotic resistance. The development of  
19 resistance is likely to occur under the selective pressure exerted by antibiotic use (7). The observed  
20 differences in resistance may be attributed to differences in antibiotic (29). The guidelines for use of  
21 antibiotics for common respiratory infections recommended by the Chilean National Health Service  
22 have not changed in Temuco, where most patient care is delivered at clinics following these guidelines  
23 (14). Sale of antibiotics without prescription is not allowed and antibiotics are generally restricted by  
24 prescribing physicians. This may explain why there has not been a steady increase in antibiotic  
25 resistance in this area.

1 **Vaccine coverage** is 61% for the available 7-valent conjugate vaccine in our survey area which is  
2 relatively low. Overall, this vaccine covers 70% of infections. However, this coverage decreases with  
3 age, as seen in our study (12) reaching only 29% coverage in elderly  $\geq 65$  years of age. Our results  
4 confirm that information concerning the sero-epidemiology of pneumococcal disease in different areas  
5 of the world is essential for the formulation of widely applicable conjugate vaccines (28).

6  
7 **Summary and conclusions.** The observations made in this 10-year survey are relevant for prevention  
8 strategies, antibiotic usage, and vaccine design. Current recommendations for conjugate multivalent  
9 vaccine formulations are based on serotypes and serogroup distribution for invasive and sterile-site  
10 pneumococcal infections in young children and infants (28). Conjugated vaccines are recommended for  
11 children under five years of age (4).

12  
13 One important observation is that serotypes 4, 9V, and 18C, three of the 7 valent conjugate vaccine  
14 serotypes, caused  $\leq$  five infections in children under five years of age in our study population in  
15 Temuco, Chile. Continued surveillance of pneumococcal infections at different ages is necessary to  
16 design the most effective vaccines to be used at the most appropriate ages. The spontaneous variability  
17 in serotype isolation observed in this surveillance is of interest. Sensitive techniques like MLST  
18 (multilocus sequence typing for follow-up of clones) will be used in the future to track these changes.  
19 (22, 26)

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**Table 1. Frequency of infections due to different pneumococcal serotypes in 10 year period (1994-2004) in Temuco, Chile**

2

Danish	<2	2-4	5-14	15-44	45-64	≥65	Total
1	14	6	13	14	13	7	67
2							
3			3	2	16	15	36
4	1	1		1	1	4	8
5	8	4	5	5	7	3	32
6A	5	1	1	1	3	3	14
6B	14	2	2	1	4	3	26
7A					1		1
7F	2		3	6	5	10	26
8			2	1	3	3	9
9A	1				1		2
9L					1		1
9N				1	3	3	7
9V	3	2		2	5	1	13
10A	1			1	4	1	7
10B						1	1
10F				1			1
11A		1	2	2			5
11F				1			1
12F	2	1	3	5	8	3	22
12B					2	1	3
13			1	3	5	2	11
14	9	1	7	5	5	7	34
15A	1				1	1	3
15B	1			1	4	2	8
15C	1	1	2	1	1	2	8
16			3	2	5	1	11
17F			1	1	1	2	5
18A	1				2	1	4
18C	2	2	1		2	3	10
18F				1	1	1	3
19A	2	1	2		2	6	13
19F	9	3	2	2	6	5	27
20	1		1		3		5
21	1						1

Danish	<2	2-4	5-14	15-44	45-64	≥65	Total
22A						1	1
22F	1		1		2	2	6
23A						2	2
23B				1		1	2
23C					1		1
23F	7	5	3	1	1	5	22
24A					1		1
24F			1				1
25					1		1
27	1					2	3
28F	1						1
29				1		1	2
31	1				1	1	3
33							
33F	3			2	1		6
34	1		1			1	3
35A					3	1	4
35B					2	4	6
35F	1	1			3	3	8
36					2	1	3
37		1					1
38					1	3	4
47F						1	1
48			1	1			2
<b>TOTAL</b>	<b>95</b>	<b>33</b>	<b>61</b>	<b>66</b>	<b>134</b>	<b>120</b>	<b>509</b>

Number of strains. Serotype 2 is included in the 23-valent vaccine but was never isolated.

1  
2  
3  
4

**Table 2. Coverage of vaccine serotypes in 10 year period (1994-2004) in Temuco, Chile**

1

2

Vaccine	Age Groups					
	<2	2-4	5-14	15-44	45-64	>65
<b>*7 Valent</b>	45/95 (42%)	16/33 (49%)	15/61 (25%)	12/66 (18%)	24/134 (18%)	28/120 (23%)
† <b>Range</b>	40-60%	40-63%	11-50%	8-30%	5-28.1%	13-41%
<b>+With cross reactivity</b>	51/85 (53%)	17/33 (52%)	16/61 (26%)	13/66 (20%)	27/134 (20%)	31/120 (26%)
<b>**10 Valent</b>	69/95 (73%)	26/33 (79%)	36/61 (58%)	37/66 (56%)	50/134 (37%)	48/120 (40%)
<b>Range</b>	60-82%	50-89%	50-86%	46-64%	16-66%	26-50%
<b>With cross reactivity</b>	74/95 (78%)	27/33 (81%)	37/61 (61%)	38/66 (58%)	53/134 (37%)	51/120 (43%)
<b>***13 Valent</b>	26/95 (80%)	26/33 (85%)	42/61 (69%)	40/66 (61%)	71/134 (53%)	72/120 (60%)
<b>Range</b>	70-82%	50-81%	50-83%	46-71	32-81	43-65%
<b>23 Valent no cross</b>	80/95 (84%)	29/33 (88%)	51/61 (84%)	51/66 (77%)	96/134 (72%)	85/120 (71%)
<b>Range</b>	84-100%	71-93%	71-93%	62-81	53-88%	61-86%
<b>With cross reactivity</b>	85/95 (90%)	30/33 (81%)	52/61 (85%)	52/66 (79%)	99/134 (74%)	88/120 (73%)

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\*7 Valent: 4,6B, 9V, 14, 18C, 19F and 23F.

\*\*10 Valent: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

\*\*\*13 Valent: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

† Range = range for each of the two-year periods.

+With cross reactivity includes coverage of serotype 6A infections.