INVASIVE PNEUMOCOCCAL DISEASE IN NEW ZEALAND, 2008

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SUMMARY

In June 2008, invasive pneumococcal disease (IPD) became a vaccine-preventable disease in New Zealand with the addition of the 7-valent pneumococcal conjugate vaccine (PCV-7), Prevenar®, to the New Zealand childhood immunisation schedule.

Since IPD was not a notifiable disease in New Zealand until 17 October 2008, the national surveillance of IPD in 2008, as in previous years, was laboratory based. For this laboratory-based surveillance, diagnostic microbiology laboratories are requested to refer all invasive isolates of *Streptococcus pneumoniae* to ESR for serotyping and antimicrobial susceptibility testing. In addition and less frequently, laboratories refer sterile site specimens to ESR to test for the presence of pneumococcal DNA by PCR (polymerase chain reaction). A case of IPD is defined as the isolation of *S. pneumoniae* from, or the detection of pneumococcal DNA in, CSF, blood or another normally sterile site.

In 2008, laboratory-based surveillance identified 631 IPD cases: 629 of which were culture positive and 2 of which were identified by the presence of pneumococcal DNA in a sterile site specimen. Two distinct isolates were identified from one of the culture-positive cases.

The annual incidence rate of IPD in 2008 was 14.8 per 100 000, with the highest age-specific rates in infants <2 years of age (62.9 per 100 000) and the elderly ≥85 years of age (80.0 per 100 000). Between 2007 and 2008, the all-age rate of IPD increased 13.0%. Some of this apparent increase may be the result of more complete referral of invasive isolates to ESR due to heightened awareness of the disease following the addition of PCV-7 to the national immunisation schedule in the middle of the year and the inclusion of IPD on the schedule of notifiable diseases later in the year.

In contrast to the increase in the all-age incidence rate of IPD, there were decreases of 26.0% and 40.9%, respectively, in the <1 year and 1 year age groups between 2007 and 2008. At this stage, it is difficult to attribute the decrease in IPD in the <1 year age group to the introduction of PCV-7 immunisation in 2008, as an even greater decrease (36.1%) was recorded between 2006 and 2007. Similarly, the decrease in IPD in 2008 in the 1 year old age group cannot be attributed to PCV-7 immunisation, unless through herd immunity, as infants in this age group were not eligible for immunisation. The proportion of disease in <2 year old infants in 2008 due to one of the serotypes included in PCV-7 was very similar to that in earlier years, which also suggests that the decrease in IPD in this age group may not be due in any great part to PCV-7 immunisation.

There were some regional differences in the incidence of IPD in 2008. The rate in the Southern region was significantly lower than that in any other region and the rate in the Midland region was significantly higher than that in the Northern region.

In infants <2 years old, 83.3% of IPD cases were due to PCV-7 serotypes and 91.0% were due to a serotype included in the 13-valent conjugate vaccine (PCV-13). The most prevalent non-PCV-7 serotype in infants was type 19A which accounted for 6.4% of cases. Over the last 5

continued

SUMMARY *continued*

years there have been no significant changes ($P \leq 0.05$) in the proportion of IPD in infants caused by any of the PCV-7 serotypes or type 19A.

The most notable change in serotypes in recent years has been a highly significant increase in serotype 1 disease, but only in the older age groups. This serotype accounted for 1.0% of IPD cases in the 5-64 year age group in 2004 but 19.2% by 2008 ($P < 0.0001$). More specifically, serotype 1 accounted for 42.9% of IPD in the 5-14 year age group in 2008, 37.9% in 15-24 year olds and 31.3% in 25-34 year olds.

In 2008 the CLSI interpretive criteria for pneumococcal penicillin MICs were redefined, with the introduction of different criteria for the parenteral treatment of meningitis, the parenteral treatment of non-meningitis infections, and the oral treatment of non-meningitis infections. 22.1% of isolates from IPD cases in 2008 were categorised as resistant when the meningitis interpretive criteria (MIC ≥ 0.12 mg/L) were applied. No isolates were categorised as resistant when the interpretive criteria for the parenteral treatment of non-meningitis (MIC ≥ 8 mg/L) were applied. 5.1% of isolates were cefotaxime resistant according to the CLSI meningitis interpretive criteria and 2.1% were resistant according to the non-meningitis interpretive criteria. There has been no overall increase in penicillin resistance over the last 10 years, although there has been some year-to-year variation. Contrary to this, there has been a trend of increasing cefotaxime resistance.

89.9% of the penicillin-resistant isolates (meningitis interpretation), 93.8% of the cefotaxime-resistant isolates (meningitis interpretation), and 89.2% of the isolates multiresistant to penicillin and at least 3 other antibiotic classes, were serotypes included in PCV-7. Among cases <2 years of age, all penicillin-resistant and cefotaxime-resistant isolates were serotypes included in PCV-7.

From 2009, surveillance reports on IPD in New Zealand will be based on IPD notification data, and supplemented with serotype and antimicrobial susceptibility data from the laboratory-based surveillance. Information only available from notification data will enable additional, important analyses of the epidemiology of IPD in this country that have not been possible with the laboratory-based surveillance of IPD. These analyses include disease rates by ethnicity, the spectrum of disease presentation, case-fatality rates, analysis of risk factors, and the vaccination status of cases.

1. INTRODUCTION

For many years the national surveillance of invasive pneumococcal disease (IPD) in New Zealand has been laboratory based, with diagnostic laboratories referring invasive isolates of *Streptococcus pneumoniae* to ESR for serotyping and antimicrobial susceptibility testing.

Based on this surveillance, information on the epidemiology of IPD, serotypes and antimicrobial susceptibility has been published periodically.[1-5] In addition, since 2002, annual reports on the antimicrobial susceptibility of isolates from IPD cases have been published on ESR's surveillance website at http://www.surv.esr.cri.nz/antimicrobial/streptococcus_pneumoniae.php.

On 1 June 2008, the 7-valent pneumococcal conjugate vaccine (PCV-7), Prevenar®, was added to the New Zealand childhood immunisation schedule. In order to enhance its surveillance, IPD became a notifiable disease on 17 October 2008. However, the information in this first annual report is based solely on data from the laboratory-based surveillance of IPD in 2008, since the disease was only notifiable for such a small proportion (ie, the last 2.5 months) of the year. From 2009, surveillance reports on IPD in New Zealand will be based on notification data and supplemented with serotype and antimicrobial susceptibility data from the laboratory-based surveillance.

2. METHODS

2.1 Surveillance methods

Diagnostic microbiology laboratories in New Zealand are requested to refer all invasive isolates of *S. pneumoniae* (ie, isolates from cerebrospinal fluid (CSF), blood or other normally sterile site) to ESR. In addition and less frequently, laboratories refer sterile site specimens to ESR to test for the presence of pneumococcal DNA by PCR.

For this laboratory-based surveillance, a case of IPD is defined as the isolation of *S. pneumoniae* from, or the detection of pneumococcal DNA in, CSF, blood or another normally sterile site. Pneumococcal isolates of the same serotype that are isolated from the same patient within a short period are considered as duplicate isolations and are not counted as a new case.

Information available about cases is usually limited to a patient identifier, patient age and sex, and the site from which the organism was isolated or the specimen type. The location of the referring laboratory is used to assign a case to a district health board (DHB) and region, as the address of the patient is not usually known. In addition, for the DHB analyses, the three DHBs in the greater Auckland area (Waitemata, Auckland and Counties Manukau) are combined, as the precise DHB cannot be ascertained from laboratory-based surveillance. Similarly, the Canterbury and South Canterbury DHBs are combined.

The 2006 census population data was used to calculate incidence rates for 2006. For the other years, the mid-year New Zealand population estimates for the relevant year were used.

Statistical analyses are performed with SAS software v.9.1.2 (SAS Institute Inc, Cary, NC, USA). The chi-square test or Fisher's exact test, as appropriate, are used to determine the significance of any observed differences. Poisson regression analysis is used to determine whether there are significant trends over time. An associated P value ≤ 0.05 is used to identify whether a difference or trend is significant.

2.2 Laboratory methods

Confirmation of isolates as *S. pneumoniae*: Referred isolates are confirmed as *S. pneumoniae* using optochin testing, demonstration of alpha-haemolysis on blood agar, and the bile solubility test.

Detection of pneumococcal DNA in clinical specimens: The presence of pneumococcal DNA in clinical specimens is detected by polymerase chain reaction (PCR).

Strain typing: *S. pneumoniae* isolates are serotyped by the capsular antigen reaction (Neufeld test) using the Danish system of nomenclature and sera obtained from the Statens Serum Institut.[6] Methods have not been established at ESR to identify the strain type when only pneumococcal DNA, rather than an isolate, is available. Therefore, the serotype can only be determined for culture-positive IPD cases.

Antimicrobial susceptibility testing: The penicillin, cefotaxime and moxifloxacin susceptibilities of *S. pneumoniae* isolates are determined by Etest (AB Biodisk, Solna, Sweden), using Mueller-Hinton agar with 5% sheep blood and incubation for 16-20 hours in 5% CO_2. Chloramphenicol, clindamycin, co-trimoxazole, erythromycin, tetracycline and vancomycin susceptibilities are determined by the Clinical and Laboratory Standards Institute's (CLSI's) disc susceptibility testing method.[7] Inducible clindamycin resistance is detected by the D-zone test.[8]

All minimum inhibitory concentrations (MICs) and zone diameters were interpreted according to the 2008 CLSI standards.[8] In this standard, the interpretive criteria for pneumococcal penicillin MICs were redefined, with the introduction of different criteria for the parenteral treatment of meningitis, the parenteral treatment of non-meningitis infections, and the oral treatment of non-meningitis infections. Different cefotaxime interpretive standards for meningitis and non-meningitis infections were introduced in 2002.

In this report, the 2008 redefined penicillin interpretive standards have been retrospectively applied to historical MIC data so that time trends are comparable. Also, in this report, when associations between penicillin or cefotaxime resistance and patient demographics, geographical distribution or serotypes are made, the meningitis interpretive standards have been used.

Multidrug resistance is defined as resistance to three antibiotics in addition to penicillin. For the purposes of this definition, the meningitis interpretive standards are used for both penicillin and cefotaxime.

2.3 Abbreviations

PCV-7: 7-valent pneumococcal conjugate vaccine with serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.
PCV-10: 10-valent pneumococcal conjugate vaccine with serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.
PCV-13: 13-valent pneumococcal conjugate vaccine with serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
PPV-23: 23-valent pneumococcal polysaccharide vaccine with serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.

3. RESULTS

In 2008, laboratory-based surveillance identified 631 IPD cases: 629 of which were culture positive and 2 of which were identified by the presence of pneumococcal DNA in a sterile site specimen. Two distinct isolates were identified from one of the culture-positive cases. The analyses in this report on the incidence of IPD, and the age, sex and geographic distribution of cases, are based on the total 631 cases. The analyses of serotypes and antimicrobial susceptibility are based on the 629 culture-positive cases, but include the two distinct isolates from the same case, and therefore these analyses are based on 630 isolates.

3.1 Disease incidence

The age and sex distribution of the 2008 cases is presented in Table 1, along with the incidence rate for each age group. The highest rates of disease were in infants <2 years of age and the elderly ≥75 years of age. There was an overall excess of males among cases. This excess was greatest in cases <5 years of age, with a male to female ratio of 2.1:1 in this age group.

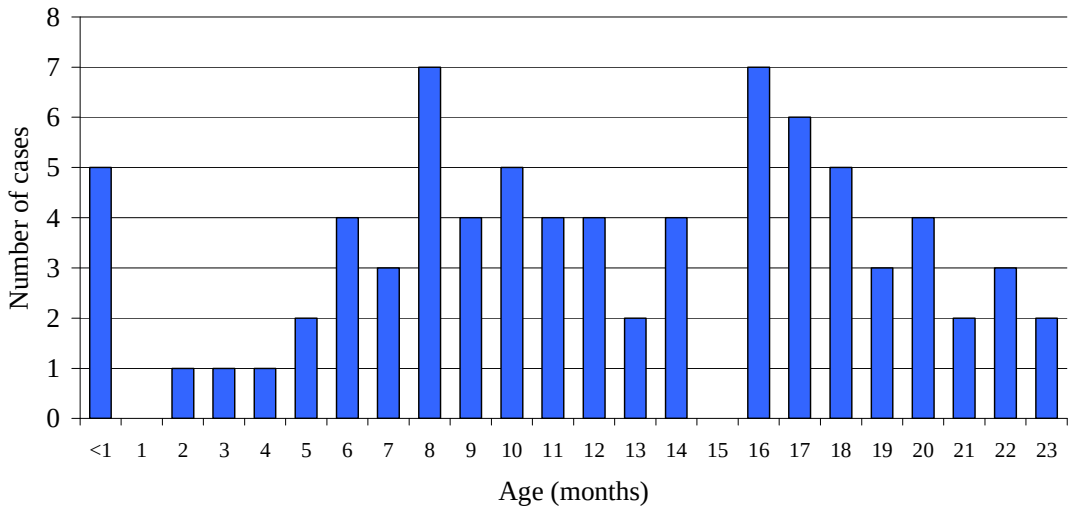
A further breakdown of the age distribution of the cases <2 years of age is shown in Figure 1.

Table 1. Numbers and rates of invasive pneumococcal disease cases by age group and sex, 2008

Age group (years)	Female	Male	All cases		
	Number	Number	Number	Percent	Rate[2]
<1	10	27	37	5.9	57.7
1	17	25	42	6.7	68.2
<2[1]	27	52	79	12.5	62.9
2-4	10	25	35	5.6	20.1
<5[1]	37	77	114	18.1	38.0
5-14	16	19	35	5.6	5.9
15-24	13	16	29	4.6	4.7
25-34	18	14	32	5.1	5.9
35-44	33	20	53	8.4	8.5
45-54	25	30	55	8.7	9.2
55-64	41	46	87	13.8	19.1
65-74	46	41	87	13.8	29.8
75-84	41	47	88	14.0	48.3
≥85	27	24	51	8.1	80.0
All ages	297	334	631	100	14.8

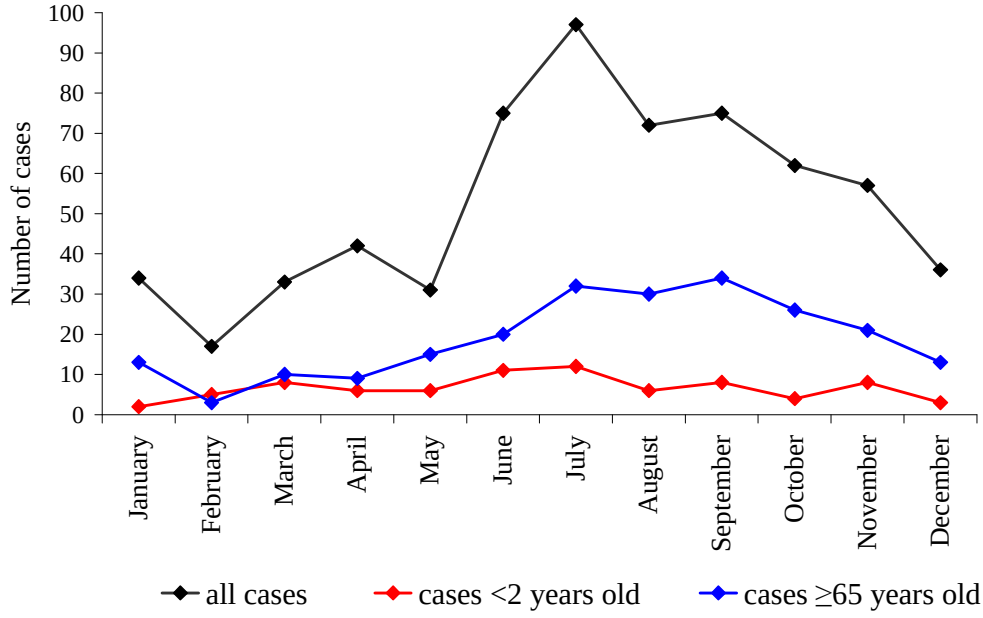
1 Shaded rows indicate composite age groups.
2 Annual incidence rate per 100 000.

Figure 1. Age distribution among invasive pneumococcal disease cases <2 years old, 2008



IPD showed the usual seasonality in 2008, with a marked peak of cases in the winter months, although this peak is less evident in the younger age group (Figure 2).

Figure 2. Seasonality of invasive pneumococcal disease, 2008



The all-age rate of IPD in 2008 (14.8 per 100 000) was the highest recorded in the last 5 years, 2004-2008, and there was a significant increase in the rate over this period (Table 2). The rate of IPD increased by 13.0% between 2007 and 2008. Over the 5 years, case numbers ranged from a low of 496 in 2005 to a high of 631 in 2008.

Contrary to the apparent all-age increase in IPD rates between 2004 and 2008, there were significant decreases in the <1 and 1 year age groups during the same years. The rate in the <1 year age group decreased 36.1% between 2006 and 2007 and a further 26.0% between 2007 and 2008 (Table 2). The rate in the 1 year age group decreased 40.9% between 2007 and 2008.

Table 2. Rates of invasive pneumococcal disease by age group, 2004-2008

Age group (years)	Annual incidence rate per 100 000					
	2004[2]	2005	2006	2007	2008	2004-8 average
<1	109.5	91.6	122.0	78.0	57.7	91.0
1	119.6	107.8	86.8	115.4	68.2	99.0
<2[1]	114.5	99.7	104.6	96.2	62.9	94.9
2-4	19.5	23.3	18.9	23.3	20.1	21.0
<5[1]	57.4	54.3	53.8	53.4	38.0	51.2
5-14	3.3	3.8	3.3	4.9	5.9	4.3
15-24	3.7	1.5	2.5	3.1	4.7	3.1
25-34	3.3	4.2	2.9	4.4	5.9	4.1
35-44	5.1	4.5	8.5	6.3	8.5	6.6
45-54	7.3	7.1	7.4	6.3	9.2	7.5
55-64	15.7	14.0	13.0	14.3	19.1	15.3
65-74	27.3	18.8	24.3	30.5	29.8	26.2
75-84	46.5	42.8	38.3	40.5	48.3	43.3
≥85	74.6	67.4	58.6	42.7	80.0	64.6
All ages	13.5	12.1	12.6	13.1	14.8	13.2

1 Shaded rows indicate composite age groups.
2 Age not known for one 2004 case.

3.2 Site of isolation

Among the 631 cases in 2008, the pneumococcus was isolated from, or detected in, blood in 589 (93.3%) cases, CSF in 20 (3.2%) cases, and other sterile sites and fluids in the remaining 22 (3.5%) cases.

3.3 Incidence by district health board

Table 3 shows the number of cases by age group and incidence rates in each region and DHB. Care should be taken with comparing the DHB rates, as some DHBs had relatively small numbers of cases. The rate of IPD in the Southern region was significantly lower than that in any other region and the rate in the Midland region was significantly higher than that in the Northern region.

Table 3. Invasive pneumococcal disease cases by region, district health board (DHB) and age group, 2008

	Number of cases by age group (years)					Rate[2]
Region and DHB[1]	**<2**	**<5**	**5-64**	**≥65**	**all ages**	**(all ages)**
Northern	**30**	**45**	**109**	**76**	**230**	**14.5**
Northland	2	2	7	5	14	9.0
Auckland[3]	28	43	102	71	216	15.1
Midland	**23**	**33**	**68**	**54**	**155**	**19.0**
Waikato	11	18	27	26	71	19.9
Lakes	3	3	2	4	9	8.9
Bay of Plenty	6	9	18	14	41	20.0
Tairawhiti	2	2	12	0	14	30.5
Taranaki	1	1	9	10	20	18.6
Central	**19**	**25**	**77**	**49**	**151**	**15.4**
Hawke's Bay	5	6	26	12	44	28.7
Whanganui	1	1	3	2	6	9.5
MidCentral	3	3	7	7	17	10.3
Hutt	3	5	9	6	20	14.1
Capital and Coast	5	6	22	12	40	14.1
Wairarapa	0	1	3	4	8	20.1
Nelson Marlborough	2	3	7	6	16	11.8
Southern	**7**	**11**	**37**	**47**	**95**	**10.8**
West Coast	0	0	0	0	0	-
Canterbury[4]	6	9	23	25	57	10.3
Otago	1	2	11	16	29	15.5
Southland	0	0	3	6	9	8.1
New Zealand total	**79**	**114**	**291**	**226**	**631**	**14.8**

1 The DHB was assigned on the basis of the location of the laboratory referring the isolate or specimen.
2 Annual incidence rate per 100 000.
3 The three DHBs in the Auckland area are combined as the precise DHB cannot be ascertained from laboratory-based surveillance.
4 Canterbury and South Canterbury DHBs are combined under the Canterbury.

3.4 Serotype distribution

Table 4 shows, for the different age groups, the proportions of the 2008 IPD cases caused by each of the serotypes included in the 7, 10 and 13-valent pneumococcal conjugate vaccines and any other serotypes that accounted for ≥1% of cases. A full list of the serotypes of all cases is presented in the Appendix. The majority (83.3%) of IPD in infants <2 years old in 2008 was due to one of the seven serotypes covered by PCV-7 (Table 4).

Table 4. Serotypes among invasive pneumococcal disease cases and vaccine coverage by age group, 2008

Serotype	Proportion (%) of IPD cases within the age group (years) due to the serotype:					
	<2 (n=78)	**2-4** (n=34)	**<5**[1] (n=112)	**5-64** (n=291)	**≥65** (n=227)	**All ages** (n=630)
Serotypes in PCV-7:						
4	6.4	5.9	6.3	11.3	9.3	9.7
6B	26.9	11.8	22.3	3.1	7.1	7.9
9V	3.9	2.9	3.6	6.5	7.9	6.5
14	26.9	29.4	27.7	10.0	21.2	17.1
18C	7.7	0.0	5.4	2.8	3.5	3.5
19F	7.7	14.7	9.8	5.2	7.1	6.7
23F	3.9	5.9	4.5	5.2	7.1	5.7
Total for PCV-7 serotypes	**83.3**	**70.6**	**79.5**	**44.0**	**63.0**	**57.1**
Additional serotypes in PCV-10:						
1	1.3	11.8	4.5	19.2	4.0	11.1
5	0.0	0.0	0.0	0.0	0.0	0.0
7F	0.0	0.0	0.0	4.1	0.9	2.2
Total for PCV-10 serotypes	**84.6**	**82.4**	**83.9**	**67.4**	**67.8**	**70.5**
Additional serotypes in PCV-13:						
3	0.0	0.0	0.0	5.5	5.3	4.4
6A	0.0	5.9	1.8	1.7	1.8	1.8
19A	6.4	5.9	6.3	7.6	4.9	6.4
Total for PCV-13 serotypes	**91.0**	**94.1**	**92.0**	**82.1**	**79.7**	**83.0**
Non-PCV serotypes[2]:						
8	2.6	0.0	1.8	3.8	1.8	2.7
9N	0.0	0.0	0.0	2.1	2.2	1.8
11A	0.0	0.0	0.0	1.7	0.9	1.1
20	0.0	0.0	0.0	2.8	0.4	1.4
22F	0.0	0.0	0.0	1.7	4.4	2.4
33F	1.3	0.0	0.9	0.7	3.1	1.6
other types	5.1	5.9	5.4	5.2	7.5	6.0

1 Shaded column indicates a composite age group.

2 The specific serotypes listed are those that accounted for ≥1% of all cases. See the Appendix for a full list of all serotypes.

The serotypes causing IPD over the last 5 years, 2004-2008, in the different age groups is shown in Table 5. Over this period, the proportion of IPD in infants <2 years old that was due to PCV-7 serotypes has been quite consistent: 82.0%, 85.8%, 85.7, 81.9%, and 83.3% for each of the years 2004 to 2008.

Table 5. Serotypes among invasive pneumococcal disease cases and vaccine coverage by age group, 2004-2008

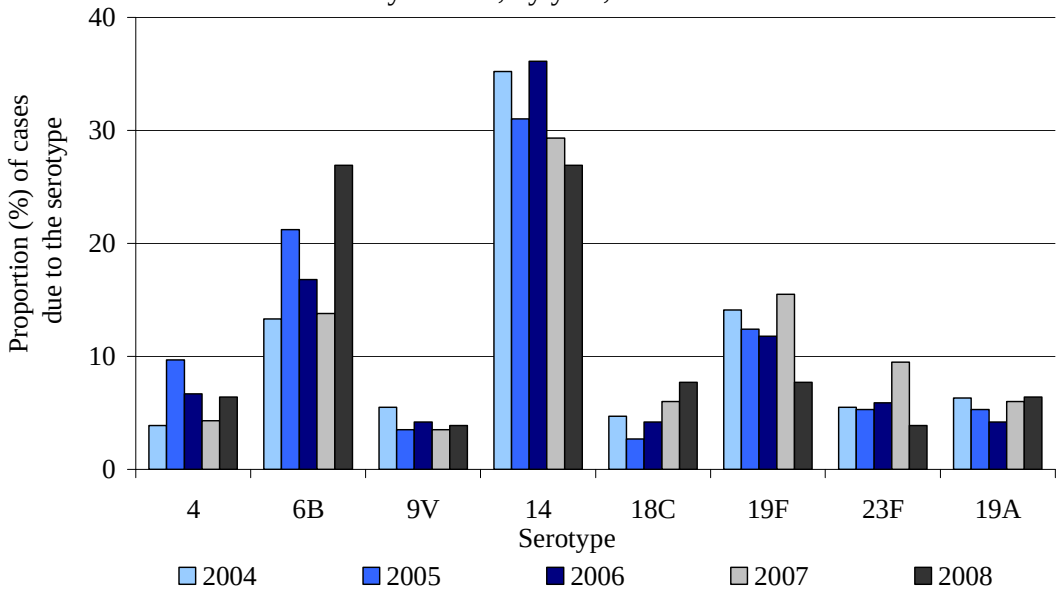
Serotype	Proportion (%) of IPD cases within the age group (years) due to the serotype:					
	<2 (n=554)	**2-4** (n=178)	**<5** (n=732)[1]	**5-64** (n=1076)	**≥65** (n=935)	**All ages** (n=2744)[2]
Serotypes in PCV-7:						
4	6.1	3.9	5.6	15.1	10.9	11.1
6B	17.7	14.0	16.8	5.4	6.4	8.8
9V	4.2	3.9	4.1	6.5	7.7	6.3
14	32.1	27.5	31.0	13.3	20.5	20.5
18C	4.9	9.0	5.9	4.3	2.6	4.1
19F	12.6	10.7	12.2	5.0	7.2	7.7
23F	6.1	6.7	6.3	5.1	7.6	6.3
Total for PCV-7 serotypes	**83.8**	**75.8**	**81.8**	**54.7**	**62.9**	**64.7**
Additional serotypes in PCV-10:						
1	0.9	2.8	1.4	8.9	1.7	4.5
5	0.0	0.0	0.0	0.0	0.1	0.04
7F	0.9	0.6	0.8	3.7	1.4	2.2
Total for PCV-10 serotypes	**85.6**	**79.2**	**84.0**	**67.3**	**66.1**	**71.3**
Additional serotypes in PCV-13:						
3	0.5	0.6	0.6	5.4	6.7	4.6
6A	2.2	6.2	3.1	2.2	1.6	2.3
19A	5.6	8.4	6.3	5.3	4.7	5.4
Total for PCV-13 serotypes	**93.9**	**94.4**	**94.0**	**80.2**	**79.1**	**83.5**
Non-PCV serotypes[3]:						
8	0.7	0.0	0.6	5.0	2.0	2.8
9N	0.2	0.0	0.1	2.0	2.8	1.8
11A	0.4	0.6	0.4	1.5	1.7	1.3
20	0.0	0.0	0.0	1.7	1.4	1.2
22F	0.5	1.1	0.7	2.9	4.1	2.7
other types	4.3	3.9	4.2	6.8	8.9	6.8

1 Shaded column indicates a composite age group.
2 Age not known for one serotype 20 case.
3 The specific serotypes listed are those that accounted for ≥1% of all cases.

Currently, the 23-valent pneumococcal conjugate vaccine (PPV-23) is recommended for people ≥65 years of age. Over the 5-year period, 2004-2008, 93.5% of the cases in this age group were one of the PPV-23 serotypes.

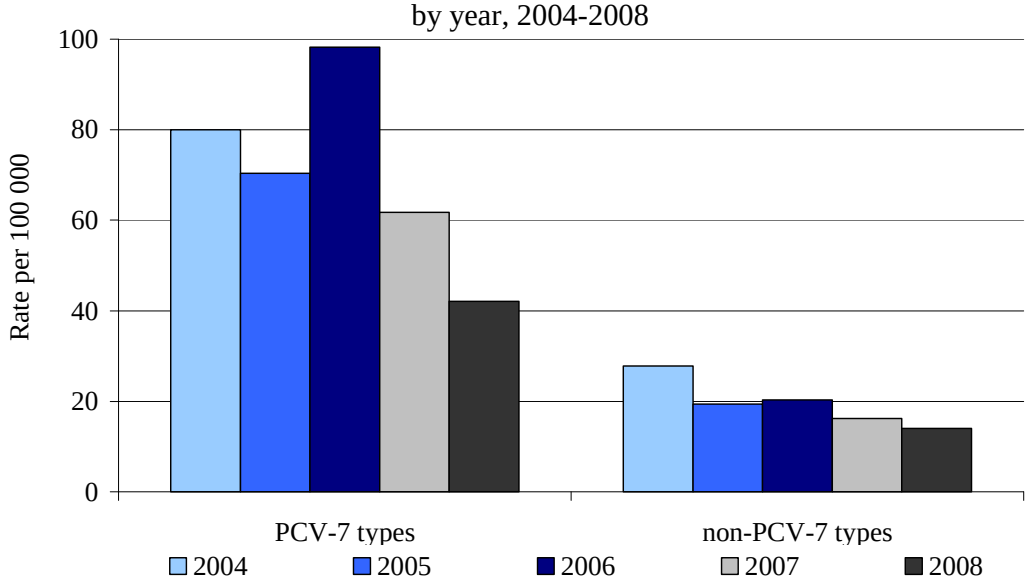
Figure 3 shows the proportion of IPD cases in infants <2 years old due to each of the serotypes included in PCV-7 and serotype 19A in each successive year in the 2004-2008 period. Over these 5 years there were no significant changes in the proportion of disease caused by any of these serotypes in this age group.

Figure 3. Serotypes among invasive pneumococcal disease cases <2 years old, by year, 2004-2008



While there have been no significant changes in the proportion of IPD cases due to PCV-7 serotypes in infants <2 years old, commensurate with the decreases in the rate of IPD in the <1 year age group in 2007 and 2008 (Table 2), the rate of disease caused by PCV-7 serotypes decreased in these years, as did the rate of disease caused by non-PCV-7 serotypes (Figure 4).

Figure 4. Rates of invasive pneumococcal disease caused by PCV-7 serotypes and non-PCV-7 serotypes, in <1 year olds, by year, 2004-2008



The most notable change in serotypes over the 2004-2008 period was a highly significant increase in serotype 1 disease, but only in the older age groups. This serotype accounted for 1.0% of IPD cases in the 5-64 year age group in 2004 but 19.2% by 2008 (P <0.0001). Serotype 1 was the most common serotype in this age group in 2008 (Table 4). A further break down of the 5-64 year age group shows that in 2008 serotype 1 was most prevalent in the 5-14 year age group, accounting for 42.9% of IPD, followed by the 15-24 and 25-34 year age groups, in which the serotype accounted for 37.9% and 31.3%, respectively, of IPD. In the ≥65 year age group, the increase in the prevalence of serotype 1 was less dramatic, but there was still a significant increase from 0% in 2004 to 4.0% in 2008 (P=0.0023).

3.5 Antimicrobial susceptibility

Table 6 shows the susceptibility of the 630 isolates from the 2008 cases. With the application of the new penicillin interpretive standards for parenteral treatment of non-meningitis infections, there were incongruous results for penicillin susceptibility compared with cefotaxime susceptibility (as interpreted according to the non-meningitis interpretive standards for cefotaxime). Eleven isolates were interpreted as penicillin susceptible but cefotaxime resistant, 19 isolates were penicillin susceptible but cefotaxime intermediate, and 2 isolates were penicillin intermediate but cefotaxime resistant. There were no such discrepancies with the new penicillin interpretive standards for meningitis, that is, all cefotaxime-intermediate and cefotaxime-resistant isolates (as interpreted according to the meningitis interpretive standards for cefotaxime) were penicillin resistant.

6.5% of isolates had combined penicillin (meningitis interpretation) and erythromycin resistance, and 0.3% had combined penicillin-intermediate resistance (non-meningitis interpretation) and erythromycin resistance. Among the penicillin-resistant isolates (meningitis interpretation), 26.6% (37/139) were multiresistant to ≥3 additional antibiotics, commonly co-trimoxazole, erythromycin and tetracycline with or without cefotaxime resistance.

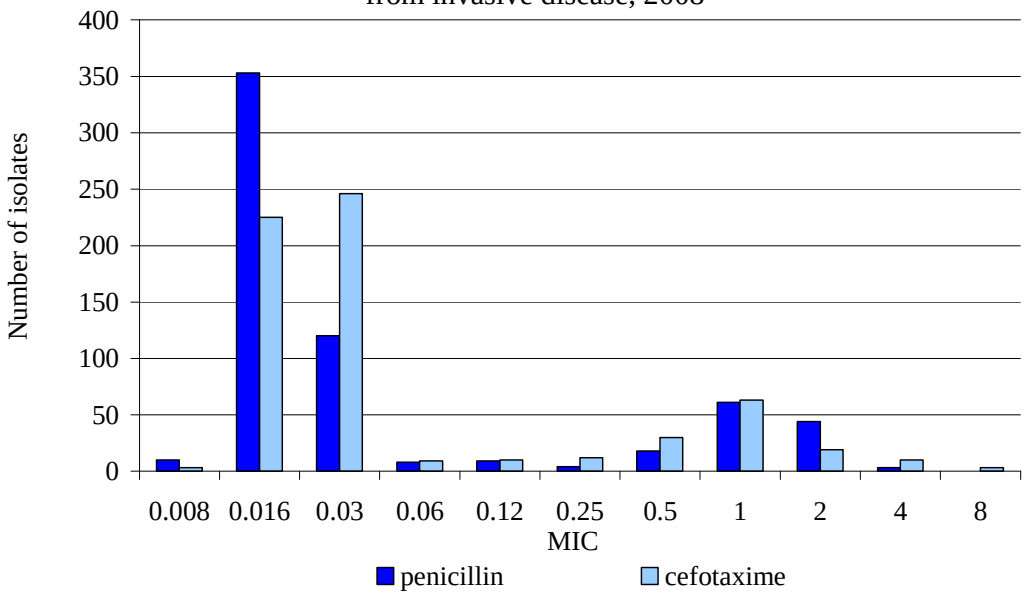
Table 6. Antimicrobial susceptibility among isolates from invasive pneumococcal disease cases, 2008

	Interpretive standards			Percent		
	S[1]	I	R			
	MIC (mg/L)			S	I	R
penicillin						
meningitis	≤0.06	-	≥0.12	77.9	-	22.1
non-meningitis	≤2	4	≥8	99.5	0.5	0.0
oral treatment	≤0.06	0.12-1	≥2	77.9	14.6	7.5
cefotaxime						
meningitis	≤0.5	1	≥2	84.9	10.0	5.1
non-meningitis	≤1	2	≥4	94.9	3.0	2.1
moxifloxacin	≤1	2	≥4	99.8	0.2	0.0
	Zone diameter (mm)					
chloramphenicol	≥21	-	≤20	97.6	-	2.4
clindamycin[2]	≥19	16-18	≤15	95.1	0.0	4.9
co-trimoxazole	≥19	16-18	≤15	67.6	2.2	30.2
erythromycin	≥21	16-20	≤15	87.8	0.3	11.9
tetracycline	≥23	19-22	≤18	91.9	0.5	7.6
vancomycin	≥17	-	-	100	-	-

1 S, susceptible; I, intermediate; R, resistant.
2 The percentage resistant given is for constitutive clindamycin resistance. A further 3 isolates (0.5%) had inducible clindamycin resistance.

Figure 5 shows the penicillin and cefotaxime MIC distribution, with the typical bimodal distribution for both antibiotics.

Figure 5. Penicillin and cefotaxime MIC distribution of pneumococci from invasive disease, 2008



Trends in penicillin susceptibility based on the meningitis interpretive standards and the non-meningitis interpretive standards, for the 10 years, 1999-2008, are shown in Figures 6 and 7, respectively. There were no significant trends ($P \leq 0.05$) over the 10 years, and there were no significant differences between the rates of penicillin resistance or intermediate resistance in 2008 compared with 1999.

Figure 6. Penicillin resistance (meningitis interpretation) among pneumococci from invasive disease, 1999-2008

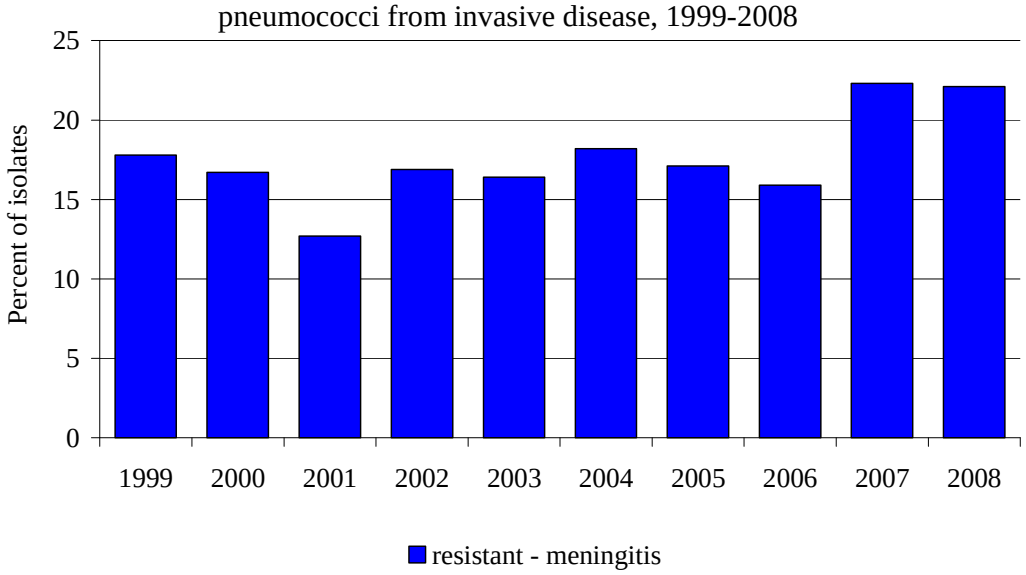
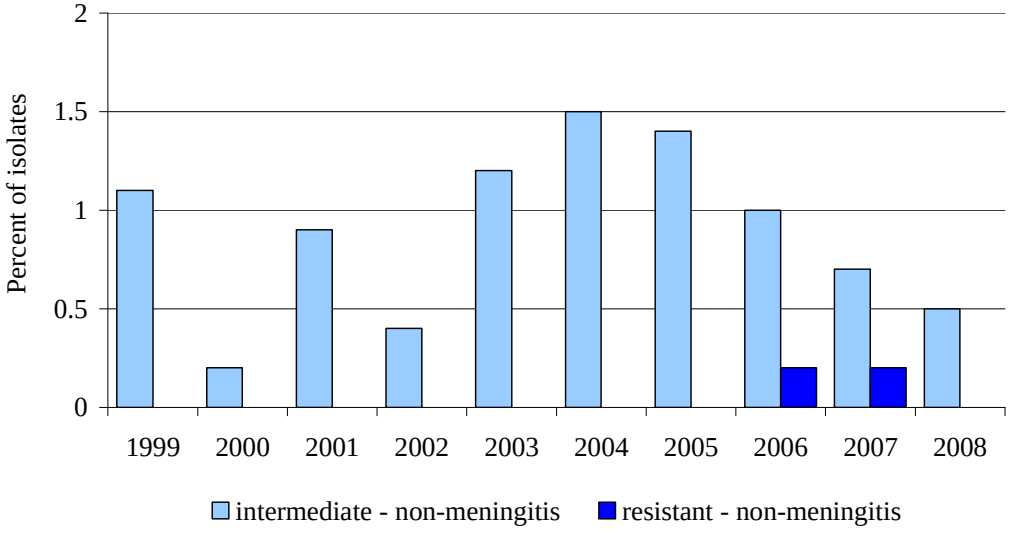


Figure 7. Penicillin intermediate resistance and resistance (non-meningitis interpretation) among pneumococci from invasive disease, 1999-2008



Trends in cefotaxime susceptibility based on the meningitis interpretive standards and the non-meningitis interpretive standards, for the 10 years, 1999-2008, are shown in Figures 8 and 9, respectively. There were significant trends over the 10 years of increasing cefotaxime resistance and intermediate resistance. Cefotaxime resistance and intermediate resistance, based on the meningitis interpretive standards, were significantly higher in 2008 than 1999, as was intermediate resistance based on the non-meningitis interpretive standards.

Figure 8. Cefotaxime intermediate resistance and resistance (meningitis interpretation) among pneumococci from invasive disease, 1999-2008

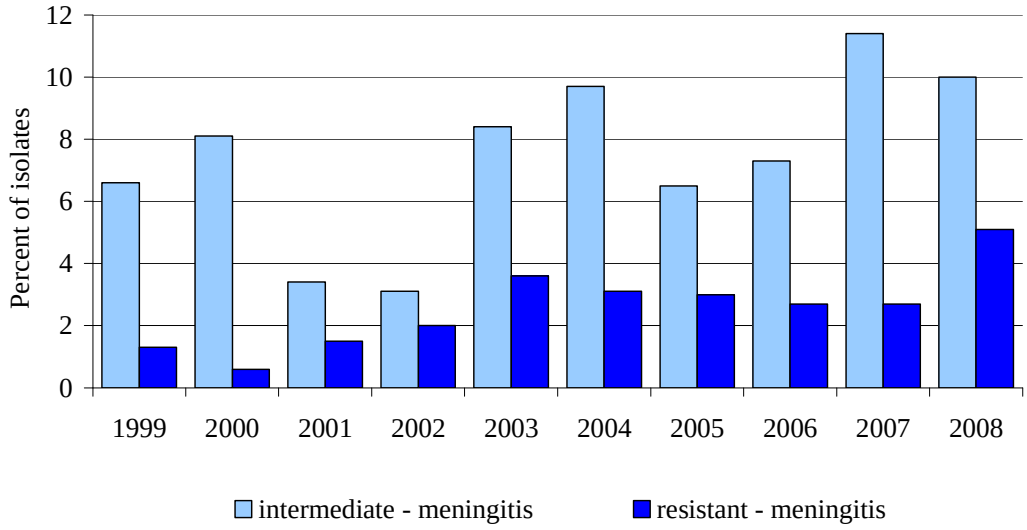
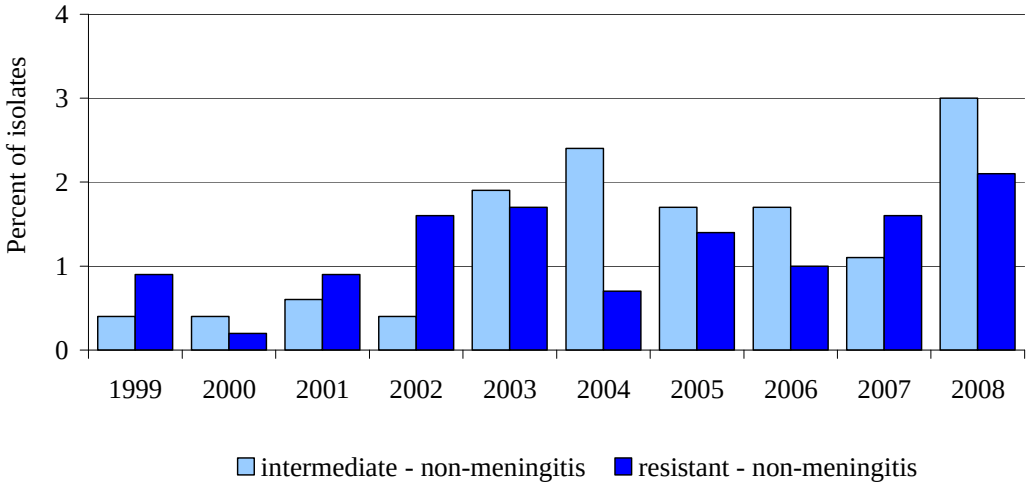


Figure 9. Cefotaxime intermediate resistance and resistance (non-meningitis interpretation) among pneumococci from invasive disease, 1999-2008



Penicillin and cefotaxime susceptibility in each DHB is shown in Table 7.

Table 7. Penicillin and cefotaxime susceptibility among isolates from invasive pneumococcal disease by region and district health board (DHB), 2008

Region and DHB[1]	Number of isolates	Penicillin	Cefotaxime	
		% resistant[2] MIC ≥0.12 mg/L	% intermediate[2] MIC 1 mg/L	% resistant[2] MIC ≥2 mg/L
Northland	**229**	**31.4**	**11.4**	**8.3**
Northland	14	7.1	0.0	0.0
Auckland[3]	215	33.0	12.1	8.8
Midland	**156**	**17.3**	**10.3**	**2.6**
Waikato	72	19.4	6.9	5.6
Lakes	9	22.2	22.2	0.0
Bay of Plenty	41	14.6	14.6	0.0
Tairawhiti	14	21.4	7.1	0.0
Taranaki	20	10.0	10.0	0.0
Central	**150**	**13.3**	**6.7**	**2.0**
Hawke's Bay	44	13.6	6.8	0.0
Whanganui	6	0.0	0.0	0.0
MidCentral	17	17.7	5.9	11.8
Hutt	20	5.0	0.0	0.0
Capital and Coast	40	10.0	10.0	0.0
Wairarapa	8	12.5	0.0	0.0
Nelson Marlborough	15	33.3	13.3	6.7
Southern	**95**	**21.1**	**11.6**	**6.3**
West Coast	0	-	-	-
Canterbury[4]	57	15.8	8.8	7.0
Otago	29	37.9	20.7	6.9
Southland	9	0.0	0.0	0.0
New Zealand total	**630**	**22.1**	**10.0**	**5.1**

1 The DHB was assigned on the basis of the location of the laboratory referring the isolate.
2 Meningitis interpretations; no intermediate category for penicillin.
3 The three DHBs in the Auckland area are combined as the precise DBH cannot be ascertained from laboratory-based surveillance.
4 Canterbury and South Canterbury DHBs are combined under the Canterbury.

Penicillin and cefotaxime susceptibility in the different age groups is shown in Table 8. There were no significant differences between age groups.

Table 8. Penicillin and cefotaxime susceptibility among isolates from invasive pneumococcal disease cases by patient age, 2008

Age group (years)	Number (%[1]) isolates		
	Penicillin	Cefotaxime	
	resistant[2] MIC ≥0.12 mg/L	intermediate[2] MIC 1 mg/L	resistant[2] MIC ≥2 mg/L
<2 (n=78)	17 (21.8)	8 (10.3)	2 (2.6)
2-4 (n=34)	11 (32.4)	3 (8.8)	4 (11.8)
5-64 (n=291)	53 (18.2)	25 (8.6)	11 (3.8)
≥65 (n=227)	58 (25.6)	27 (11.9)	15 (6.6)
All ages (n=630)	139 (22.1)	63 (10.0)	32 (5.1)

1 Percentage of the cases within the age group.
2 Meningitis interpretations; no intermediate category for penicillin.

The majority of the penicillin-resistant (meningitis interpretation) invasive pneumococci were one of the serotypes usually associated with penicillin resistance (Table 9). Nearly 90% of the penicillin-resistant isolates, and an even higher proportion of cefotaxime-intermediate and cefotaxime-resistant isolates, were serotypes included in PCV-7. Among cases <2 years of age, all penicillin-resistant, cefotaxime-intermediate and cefotaxime-resistant isolates (meningitis interpretations) were serotypes included in PCV-7.

Table 9. Serotypes among penicillin and cefotaxime resistant and intermediate, and multiresistant, isolates from invasive pneumococcal disease cases, 2008

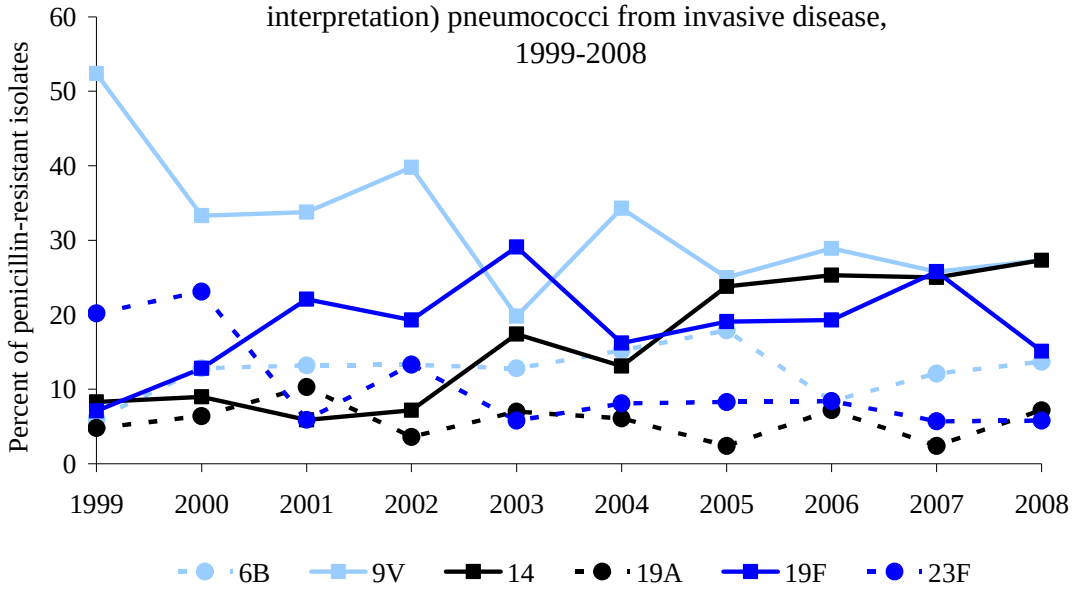
Serotype	Number (%[1]) isolates			
	Penicillin	Cefotaxime		multi-resistant[3] (n=37)
	resistant[2] MIC ≥0.12 mg/L (n=139)	intermediate[2] MIC 1 mg/L (n=63)	resistant[2] MIC ≥2 mg/L (n=32)	
Serotypes in PCV-7:				
4	1 (0.7)	0	0	0
6B	19 (13.7)	10 (15.9)	2 (6.3)	10 (27.0)
9V	38 (27.3)	26 (41.3)	0	0
14	38 (27.3)	15 (23.8)	15 (46.9)	6 (16.2)
18C	0	0	0	0
19F	21 (15.1)	4 (6.4)	12 (37.5)	15 (40.5)
23F	8 (5.8)	4 (6.4)	1 (3.1)	2 (5.4)
Total for PCV-7 serotypes	**125 (89.9)**	**59 (93.7)**	**30 (93.8)**	**33 (89.2)**
Additional serotypes in PCV-10:				
1	0	0	0	0
5	0	0	0	0
7F	0	0	0	0
Total for PCV-10 serotypes	**125 (89.9)**	**59 (93.7)**	**30 (93.8)**	**33 (89.2)**
Additional serotypes in PCV-13:				
3	0	0	0	0
6A	2 (1.4)	0	1 (3.1)	1 (2.7)
19A	10 (7.2)	3 (4.8)	1 (3.1)	3 (8.1)
Total for PCV-13 serotypes	**137 (98.6)**	**62 (98.4)**	**32 (100)**	**37 (100)**
Non-PCV serotypes				
6 non-typable	1 (0.7)	0	0	0
9N	1 (0.7)	1 (1.6)	0	0

1 Percentage of the intermediate or resistant isolates.
2 Meningitis interpretations; no intermediate category for penicillin.
3 Resistant to penicillin (meningitis interpretation) and three additional antibiotics.

Serotypes 19F and 6B accounted for the majority of the multiresistance (Table 9). Twelve of the 15 multiresistant serotype 19F isolates were cefotaxime resistant, but only 2 of the 10 multiresistant serotype 6B isolates were cefotaxime resistant. The majority (80.0%, 12/15) of the multiresistant serotype 19F isolates were resistant to at least penicillin, cefotaxime, co-trimoxazole, erythromycin and tetracycline.

Over the last 10 years, serotype 9V has been the prevalent penicillin-resistant serotype. Serotype 19F and, in more recent years serotype 14, are the other two more prevalent serotypes among penicillin-resistant invasive pneumococci (Figure 10).

Figure 10. Serotype distribution among penicillin-resistant (meningitis interpretation) pneumococci from invasive disease, 1999-2008



4. DISCUSSION

Some of the apparent increase in the incidence of IPD in 2008 may be the result of more complete referral of invasive isolates to ESR due to heightened awareness of the disease following the addition of PCV-7 to the national immunisation schedule in the middle of the year and then the inclusion of IPD on the schedule of notifiable diseases later in the year. In addition, direct laboratory notification by diagnostic laboratories to medical officers of health was introduced in 2008. This notification requirement may have served as a trigger or reminder for laboratories to refer invasive pneumococcal isolates to ESR. The last audit of the laboratory-based surveillance system in 2007 indicated that the system had a sensitivity of 89% with isolates referred to ESR from 556 of 651 IPD cases. Therefore, at least some of the 13% increase in IPD cases recorded in 2008 could be due to more complete referral of invasive isolates to ESR.

In contrast to the increase in the all-age incidence of IPD in 2008, there were decreases in the <1 year and 1 year age groups. While PCV-7 was only added to the immunisation schedule on 1 June 2008, with a catch up for children born after 1 January 2008, much of the 26% decrease in disease in 2008 in the <1 year age group could be attributable to the immediate impact of the vaccine. PCV-7 has a reported effectiveness of 73% after 1 dose in infants ≤7 months of age, which rises to 96% after two doses.[9] However, at this stage it is difficult to attribute the decrease in IPD in the <1 year age group in 2008 to universal PCV-7 immunisation, as an even greater decrease (36%) in the rate of disease in this age group was recorded between 2006 and 2007 and rate in the age group has been quite variable from year to year, possibly because of the relatively small numbers when analyses are confined to a narrow age range.

Similarly, the decrease in IPD in 2008 in the 1 year old age group cannot be attributed to universal PCV-7 immunisation, unless through herd immunity, as infants in this age group were not eligible for universal PCV-7 immunisation. The observation that the proportion of disease due to PCV-7 serotypes in <2 year old infants in 2008 (83.3%) was very similar to that in earlier years, also suggests that the decrease in IPD in this age group may not be due in any great part to PCV-7 immunisation. If the decrease in disease in 2008 was due to immunisation, it would be expected that PCV-7 serotypes would form a smaller proportion of the disease burden than prior to the introduction of the vaccine.

However, there was a significant decrease in IPD cases in Australia in the same year (2005) that universal PCV-7 immunisation was introduced, although immunisation was introduced at the beginning of the year (1 January) rather than mid-year, with a catch up for infants <2 years old. Rates of disease in the <2 year age group dropped from approx 95 per 100 000 in 2004 to approx 30 per 100 000 in 2005.[10]

Any analysis of the immediate impact of the introduction of universal infant PCV-7 immunisation in 2008 in New Zealand is complicated by the fact that this vaccine has been available and funded since 2006 for children at high risk of pneumococcal disease. Vaccination of these children may account for the some of the decrease in IPD prior to 2008 in certain age groups - for example, the decrease in the <1 year olds between 2006 and 2007 and the decrease in the 1 year old group in 2008.

PCV-7 provides good coverage (83.8%, 2004-2008) of the serotypes that are the prevalent cause of IPD in infants <2 years old in New Zealand. This figure may underestimate the potential coverage afforded by PCV-7, as there is now evidence that vaccine-induced protection against serotype 6B may also provide serogroup cross-protection against type 6A.[11] During the last 5 years, serotype 6A was the second most common non-vaccine serotype, after 19A, in the <2 year olds. The PCV-13 would provide somewhat better coverage (93.9%, 2004-2008) in this age group.

There have been reports of 'serotype replacement', an increase in disease caused by non-PCV-7 serotypes, particularly serotype 19A, in several countries following the introduction of PCV-7.[12-14] Such serotype replacement could potentially erode some of the positive impact achieved with the use of the vaccine. In this country, serotype 19A disease is already a relatively common cause of IPD in infants, and over the 2004 to 2008 period was a more common cause of IPD in infants <2 years of age than the PCV-7 serotypes 9V and 18C. The incidence of serotype 19A disease has been quite stable in New Zealand over the last 5 years. There is additional concern about the increase in disease due to this type as it is frequently associated with antibiotic resistance.[15,16]

The most notable change in the prevalence of any serotype during the last 5 years has been the increase in serotype 1 disease, particularly in school-age children and young adults. There have been several reports of outbreaks of serotype 1 disease in other countries, and specifically reports that serotype 1 has been largely responsible for increases in the incidence of empyema and complicated pneumonia in children over the last decade.[17] As our laboratory-based surveillance does not provide any comprehensive information on clinical presentation, we are unable to test the association of recent serotype 1 disease in New Zealand with any particular presentation.

The previous penicillin susceptibility breakpoints for *S. pneumoniae,* which were universally applied to all pneumococcal infections, were predicated on the need to ensure successful treatment for pneumococcal meningitis. However, it had become clear that the outcomes for pneumococcal pneumonia caused by penicillin non-susceptible strains in patients treated with parenteral penicillin were no different to those in patients treated with other antibiotics. The application of the universal breakpoints meant that many pneumococcal infections outside the central nervous system were being unnecessarily treated with newer broad-spectrum and more expensive antibiotics when penicillin would have been effective.[18] Therefore in 2008, CLSI published new interpretive standards for pneumococcal penicillin MICs and introduced different criteria for the parenteral treatment of meningitis, the parenteral treatment of non-meningitis infections, and the oral treatment of non-meningitis infections.

The application of these new interpretive criteria to the invasive pneumococci isolated in 2008, indicates that parenteral penicillin treatment should be effective for almost all (99.5%) invasive pneumococcal infections outside the central nervous system, with no isolates categorised as resistant with these criteria and only 0.5% (3/630) categorised as intermediate. In contrast, 22.1% of isolates were categorised as resistant when the meningitis criteria were applied. No matter which interpretive criteria are used, there has been no overall increase in penicillin resistance over the last 10 years, although there has been some year-to-year variation. Contrary to this, there has been a trend of increasing cefotaxime resistance.

With the changes in the penicillin interpretive criteria, and the current lack of any published data from other countries using the new criteria, the most valid comparison of penicillin resistance among invasive pneumococci in New Zealand with that in other countries is a comparison of our penicillin resistance (meningitis interpretation, MIC ≥0.12 mg/L) with penicillin non-susceptibility, as defined by the old universal criteria (MIC ≥0.12 mg/L), reported in other places. Such a comparison indicates that we have a relatively high rate of pneumococcal penicillin resistance compared, for example, with 4% non-susceptibility in the United Kingdom in 2007 and 10.6% in Australia in 2006.[19-20] In fact, our 2008 resistance rate of 22.1% was the same as the rate of non-susceptibility reported in 2007 for Spain, which was once notorious for pneumococcal resistance.[19]

PCV-7 gives good coverage of the serotypes associated with resistance. In 2008, 89% or more of the penicillin-resistant, cefotaxime-resistant and multiresistant isolates belonged to one of the PCV-7 types. Serotype 19A accounted for most of the remaining penicillin resistance and multiresistance.

To assess the impact of PCV-7 immunisation and the need to change to vaccines with extended serotype coverage as they become available, it is important to closely monitor serotypes and antibiotic resistance among invasive pneumococci for serotype replacement (including capsular switching) and any development of resistance in non-PCV-7-vaccine types. Ideally, this monitoring should extend beyond invasive isolates to nasopharyngeal isolates, as nasopharyngeal carriage with a particular serotype is a necessary pre-condition for invasive disease with that serotype.

Future enhancements to laboratory-based surveillance of IPD planned by ESR include the introduction of additional typing, including multilocus sequence typing, to further characterise the strains causing disease and, in particular, to detect capsular switching – a mechanism by which pneumococci can evade serotype-specific vaccine-induced immunity.

Future IPD surveillance reports, which will use data collected with IPD notifications, will include several additional, important analyses: IPD rates by ethnicity, the spectrum of disease presentation, case-fatality rates, analysis of risk factors, and the vaccination status of cases.

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APPENDIX

Serotypes among invasive pneumococcal disease cases by age group, 2008

Serotype	Number (% within age group) of IPD cases due to each serotype:									
	<2 (n=78)		2-4 (n=34)		5-64 (n=291)		≥65 (n=227)		All ages (n=630)	
1	1	(1.3)	4	(11.8)	56	(19.2)	9	(4.0)	70	(11.1)
3	0		0		16	(5.5)	12	(5.3)	28	(4.4)
4	5	(6.4)	2	(5.9)	33	(11.3)	21	(9.3)	61	(9.7)
6	0		0		0		1	(0.4)	1	(0.2)
6A	0		2	(5.9)	5	(1.7)	4	(1.8)	11	(1.8)
6B	21	(26.9)	4	(11.8)	9	(3.1)	16	(7.1)	50	(7.9)
7	0		0		2	(0.7)	0		2	(0.3)
7A	0		0		1	(0.3)	0		1	(0.2)
7F	0		0		12	(4.1)	2	(0.9)	14	(2.2)
8	2	(2.6)	0		11	(3.8)	4	(1.8)	17	(2.7)
9N	0		0		6	(2.1)	5	(2.2)	11	(1.8)
9V	3	(3.9)	1	(2.9)	19	(6.5)	18	(7.9)	41	(6.5)
10	0		0		0		1	(0.4)	1	(0.2)
10A	1	(1.3)	1	(2.9)	0		0		2	(0.3)
10F	0		0		1	(0.3)	0		1	(0.2)
11A	0		0		5	(1.7)	2	(0.9)	7	(1.1)
12F	0		1	(2.9)	0		0		1	(0.2)
13	0		0		0		1	(0.4)	1	(0.2)
14	21	(26.9)	10	(29.4)	29	(10.0)	48	(21.2)	108	(17.1)
17F	0		0		3	(1.0)	2	(0.9)	5	(0.8)
18B	1	(1.3)	0		1	(0.3)	2	(0.9)	4	(0.6)
18C	6	(7.7)	0		8	(2.8)	8	(3.5)	22	(3.5)
19A	5	(6.4)	2	(5.9)	22	(7.6)	11	(4.9)	40	(6.4)
19F	6	(7.7)	5	(14.7)	15	(5.2)	16	(7.1)	42	(6.7)
20	0		0		8	(2.8)	1	(0.4)	9	(1.4)
22	0		0		0		1	(0.4)	1	(0.2)
22A	0		0		0		1	(0.4)	1	(0.2)
22F	0		0		5	(1.7)	10	(4.4)	15	(2.4)
23A	0		0		2	(0.7)	4	(1.8)	6	(1.0)
23F	3	(3.9)	2	(5.9)	15	(5.2)	16	(7.1)	36	(5.7)
33F	1	(1.3)	0		2	(0.7)	7	(3.1)	10	(1.6)
34	0		0		0		1	(0.4)	1	(0.2)
35	1	(1.3)	0		1	(0.3)	1	(0.4)	3	(0.5)
37	0		0		1	(0.3)	0		1	(0.2)
38	0		0		3	(1.0)	1	(0.4)	4	(0.6)
non-typable	1	(1.3)	0		0		1	(0.4)	2	(0.3)