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## Serotype distribution in pneumococcal acute otitis media with ruptured tympanic membrane or sepsis in Germany

M. Linden, R. R. Reinert

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Title: Serotype distribution in pneumococcal acute otitis media with ruptured tympanic membrane or sepsis in Germany

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Abstract: This retrospective analysis examined the pneumococcal serotype distribution of acute otitis media in Germany from 1995 to 2007. Data from the German National Reference Centre for Streptococci included 512 cases of pneumococcal otitis media in children and adults. Infections were mainly seen in children aged <5 years, who represented 67.0% of all reported cases. Most isolates (86.7%) were from spontaneous ruptures of the tympanum; 11.1% of the isolates were from otogenic sepsis or meningitis. Serotype 19F was the leading serotype (21.5%); serotype 3 (13.9%) was also often encountered. In children aged <5 years, the 7-valent, 10-valent, and 13-valent pneumococcal conjugate vaccines covered 54.3%, 60.2%, and 84.6% of the serotypes, respectively. Reduced penicillin susceptibility (minimum inhibitory concentration  $\geq 0.1$  mg/L) was seen in 11.0% of strains; 22.4% of strains were resistant to macrolides. Although based on a very limited selection of acute otitis media isolates, this analysis provides an estimate of the pneumococcal serotypes responsible for otitis media in Germany and underscores the need for future prospective studies.

Ref.: Ms. No. EJCMID-D-09-00590

Serotype distribution in pneumococcal acute otitis media with ruptured tympanic membrane or sepsis in Germany  
European Journal of Clinical Microbiology & Infectious Diseases

Dear Dr van der Linden,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.

Your revision is due by 03-03-2010.

To submit a revision, go to <http://ejcmid.edmgr.com/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Alex van Belkum  
Editor-in-Chief  
European Journal of Clinical Microbiology & Infectious Diseases

Reviewers' comments:

Reviewer #1: This is an important collection of AOM isolates. Such collections are rare since in most countries no central collection of AOM isolates exists. Therefore, despite several important limitations of the study, some of which are recognized by the authors and some of which I have added, this set of data is important. At least serotypes associated with complicated otitis media can be assumed from this collection.

I. Abstract

1) Please provide the years of the study.

We thank the reviewer for this comment. We have added the years of the study (1995-2007) to the abstract.

2) You need to recognize already at the abstract level that this represents an important, but very selective series of isolates (since it is mainly or at least commonly non-responsive AOM, recurrent AOM, complicated AOM or invasive cases)

We agree with the reviewers and have added the following sentence to the abstract: 'Although based on a very limited selection of acute otitis media isolates,....'

II. Introduction

1) First page of the introduction lines, 14-15: There are new and more detailed references for the statement that serotypes are important in AOM (eg. Shouval et al, PIDJ 2009;28:277-282; Aguilar et al, J Pediatr Otolaryngol 73:1407-1411, 2009; Rodgers et al, Vaccine 27:3802-10, 2009).

The reviewer is right and we have added these more recent references to the text.

### III. Results

1) The inclusion of *S. pneumoniae* isolated from blood and CSF is probably not appropriate since you do not have the proof that the otitis media was pneumococcal otitis media. I believe this should be excluded.

Even though it was not microbiologically proven that AOM patients with pneumococci isolated from invasive material suffered from pneumococcal otitis, this is very likely. To emphasize this point we have added the following sentence to the manuscript: 'Even though it is highly likely that these children suffered from pneumococcal AOM, this was not microbiologically confirmed in all cases.'

2) Figure 1: Please instead of 2 categories "all ages" and "<5 years" modify those to "<5 years" and ">= 5 years".

We have modified Table 2 according to the reviewers' comments. Furthermore we have changed the age cohorts accordingly ( 0 - <2, >=2 - <5, >=5 - <16, >=16) throughout the whole text and recalculated all corresponding values for coverage, serotypes, MICs, etc. as well as Figure 2.

3) Table 2 and text" Coverage by PCV7, PCV10 and PCV13: Some assumptions with regard to coverage of PCV7 and PCV10 against 6A must be made.

All coverage data were calculated without assuming any cross-protection. A remark stating this explicitly concerning serotype 6A was added to the text: 'The coverage calculations were performed without accounting for possible cross-protection of serotype 6B towards serotype 6A, as described in some reports on PCV7 and the 10-valent vaccine'.

4) This study does not really represent all cases of AOM, but rather selected population with complicated AOM.

Therefore, the findings may not necessarily compare to other studies, many of which also have their own selection.

We fully agree with the reviewer regarding the limitations of this study, and that is why we have explicitly mentioned them in the discussion and also in the Abstract (see comment 1, 2)

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7 **Serotype distribution in pneumococcal acute otitis media with ruptured tympanic**  
8 **membrane or sepsis in Germany**

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**Abstract** This retrospective analysis examined the pneumococcal serotype distribution of acute otitis media in Germany from 1995 to 2007. Data from the German National Reference Centre for Streptococci included 512 cases of pneumococcal otitis media in children and adults. Infections were mainly seen in children aged <5 years, who represented 67.0% of all reported cases. Most isolates (86.7%) were from spontaneous ruptures of the tympanum; 11.1% of the isolates were from otogenic sepsis or meningitis. Serotype 19F was the leading serotype (21.5%); serotype 3 (13.9%) was also often encountered. In children aged <5 years, the 7-valent, 10-valent, and 13-valent pneumococcal conjugate vaccines covered 54.3%, 60.2%, and 84.6% of the serotypes, respectively. Reduced penicillin susceptibility (minimum inhibitory concentration  $\geq 0.1$  mg/L) was seen in 11.0% of strains; 22.4% of strains were resistant to macrolides. Although based on a very limited selection of acute otitis media isolates, this analysis provides an estimate of the pneumococcal serotypes responsible for otitis media in Germany and underscores the need for future prospective studies.

*Abstract Word Count:* 166

*Keywords:* pneumococcal conjugate vaccines, *Streptococcus pneumoniae*, acute otitis media, Germany

*Text Word Count:* Approximately 1850

## Introduction

*Streptococcus pneumoniae* is a major pathogen in cases of acute otitis media (AOM), along with *Haemophilus influenzae* and *Moraxella catarrhalis* [1]. Of these three organisms, *S. pneumoniae* has been associated with more severe AOM signs and symptoms, greater virulence, and more complications [2]. To date, 91 distinct serotypes of *S. pneumoniae* have been identified, but only a few are responsible for most cases of AOM in young children, including serotypes 3, 6B, 9V, 14, 19F, and 23F [3, 4].

The currently approved seven-valent pneumococcal conjugate vaccine (PCV7; Prevnar<sup>®</sup>/Prevenar<sup>®</sup> [Pfizer Inc, Philadelphia, PA]) includes purified capsular polysaccharides of seven serotypes of *S. pneumoniae* (4, 6B, 9V, 14, 18C, 19F, and 23F) conjugated to mutant diphtheria toxoid cross-reactive material (CRM)<sub>197</sub>. In prelicensure trials, PCV7 demonstrated almost 100% efficacy against invasive pneumococcal disease (IPD) and some efficacy against AOM [5]. In the Northern California Kaiser Permanente trial in the USA ( $n=37,868$  infants), PCV7 was 7% efficacious in preventing episodes of otitis media [5]. In the Finnish Otitis Media (FinOM) trial ( $n=1,662$  infants), efficacy against AOM from any cause was 6% [6]. Long-term follow-up of these cohorts confirmed that receipt of PCV7 in infancy was associated with fewer otitis media physician visits and episodes [7] and a reduction in tympanostomy tube placement in children aged <12 months to 4–5 years [7, 8]. In a more recent publication, Shouval et al. reported that in children aged <3 years in Israel, PCV7, 10-valent vaccine, and 13-valent vaccine provided coverage of AOM of 54%, 59%, and 79%, respectively [9]. In a review by Rodgers et al., serotypes 6A, 6B, 14, 19A, 19F, and 23F were described as the most common serotypes in pneumococcal AOM among children worldwide [10].

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Although vaccine trials with PCV7 showed modest efficacy against AOM overall, there was considerable variation in serotype-specific efficacy. In the FinOM trial, PCV7 reduced the incidence of AOM due to vaccine serotypes by 57% overall. However, efficacy for specific serotypes ranged from 25% for serotype 19F to 84% for serotype 6B [6].

Following generalized vaccination with PCV7 in the USA, at least three studies reported on the impact of immunization on the microbiology of AOM. These studies analyzed pre- and post-vaccination rates of middle-ear fluid (MEF) pathogen isolates and found that community use of PCV7 significantly reduced the overall proportion of *S. pneumoniae* isolates and vaccine serotypes causing AOM [11–13]. Data from the USA demonstrated that in a comparison of 2004 and 1997–1999 (baseline period), rates of ambulatory visits and antibiotic prescriptions attributable to AOM decreased by 42.7% and 41.9%, respectively [14]. Notably, the proportion of AOM infections due to nonvaccine pneumococcal strains and serogroups 6 and 19 increased over time [11, 13].

In July 2006, the German Ständige Impfkommision (permanent committee on vaccination, STIKO) recommended vaccination with PCV7 for all children aged <2 years [15]. However, little is known about the epidemiology of pneumococcal otitis media in Germany [10, 16], and no recent data are available on the serotype distribution of pneumococcal isolates from German children and adults with otitis media. Therefore, our study examined the pneumococcal serotype distribution related to AOM, using data from the German National Reference Centre for Streptococci.

## Materials and methods

The database of the German National Reference Centre for Streptococci, which contains information on more than 25,000 cases of pneumococcal infections, was searched for cases of pneumococcal otitis media that occurred between 1995 and 2007. All *S. pneumoniae* isolates

1 from ear swab and other isolates with the clinical diagnosis “acute otitis” or “mastoiditis”  
2 were included in the study. Duplicate isolates were excluded from the analysis.  
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5 Strains were obtained from (1) the study of IPD in children performed on a nation-  
6 wide basis in Germany since 1996 (collaboration between the Robert Koch Institute, the  
7 ESPED [Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland], and the  
8 National Reference Centre for Streptococci) [17–22], and (2) the nation-wide surveillance of  
9 IPDs in adults [23] and upper respiratory tract infections in children and adults [17]. All  
10 studies were summarized in one database and made available for analysis.  
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19 Pneumococcal isolates were identified with standard microbiology methods, such as  
20 determination of optochin susceptibility and bile solubility. Strains were typed using the  
21 antisera provided by the Statens Serum Institut in Copenhagen, Denmark. A subgroup of all  
22 strains was tested for antibiotic sensitivity to penicillin G and clarithromycin (macrolide)  
23 using the Clinical and Laboratory Standards Institute (CLSI) guidelines for susceptibility  
24 testing [24].  
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## 36 Results

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38 A total of 512 isolates, mainly from children aged <2 years (34.4%), were included in the  
39 study. The remainder were from children aged ≥2 to <5 years (32.6%); ≥5 to <16 years  
40 (22.5%); and adults aged ≥16 years (10.5%). Sources of pneumococcal isolates are presented  
41 in **Table 1**. Most cases (444 strains; 86.7% of isolates) were from children with spontaneous  
42 rupture of the tympanum (specimen = pus from the middle ear or ear swab). In addition, three  
43 isolates from puncture of the mastoid and eight isolates from tympanocentesis were included  
44 in the study. There were 57 isolates (11.1%) from invasive disease (sepsis and meningitis).  
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1 was not microbiologically confirmed in all cases. Infections were more often seen in males  
2 (54.5% of strains).  
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4 Serotype data for all strains are presented in **Figure 1**. In our study, 19F was the  
5 leading serotype (21.5%), followed by serotypes 3 (13.9%), 14 (10.5%), and 23F (10.0%).  
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7 Among children aged <5 years, the leading serotype was 19F (24.5%), followed by serotypes  
8 14 (12.2%), 23F (11.4%), and 3 (8.7%) (**Figure 1**).  
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10 Coverage by serotypes included in the current and investigational pneumococcal  
11 conjugate vaccine formulations was evaluated. These formulations include PCV7 (serotypes  
12 4, 6B, 9V, 14, 18C, 19F, and 23F); the 10-valent vaccine (PCV7 serotypes plus serotypes 1,  
13 5, and 7F); and the investigational 13-valent vaccine (10-valent vaccine serotypes plus  
14 serotypes 3, 6A, and 19A). Coverages of the 7-valent, 10-valent, and investigational 13-  
15 valent pneumococcal conjugate vaccines in isolates from pneumococcal AOM with ruptured  
16 tympanic membrane or sepsis in Germany are presented in **Table 2**. The coverage  
17 calculations were performed without accounting for possible cross-protection of serotype 6B  
18 towards serotype 6A, as described in some reports on PCV7 and the 10-valent vaccine [25,  
19 26]. For children aged <5 years, coverage of PCV7 was 60.3% ( $n=207$ ); the 10-valent  
20 vaccine, 63.6% ( $n=218$ ); and the 13-valent vaccine, 85.4% ( $n=293$ ). The cumulative coverage  
21 of the different pneumococcal conjugate vaccine formulations is presented in **Figure 2**.  
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23 Antibiotic susceptibility data were available for 456 isolates. Reduced susceptibility to  
24 penicillin was seen in 11.0% of strains. This included a relatively high rate of strains (4.4%)  
25 with high-level penicillin G resistance (minimum inhibitory concentration [MIC]  $\geq 2$  mg/L).  
26 The rate of resistance to macrolides (clarithromycin) was 22.4% (**Table 3**). Antibiotic  
27 susceptibility data were available for 304 strains isolated from children aged <5 years; 9.5%  
28 and 24.0% of these strains were found to be nonsusceptible to penicillin G and  
29 clarithromycin, respectively.  
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Characteristics of IPD in 33 children with otitis media (otogenic sepsis or meningitis) are presented in **Table 4**. These cases were mainly seen in very young children (aged  $\leq 1$  year). The collection included 13 cases diagnosed from cerebrospinal fluid and 20 cases from blood. Among these infections, serotype 14 was the most common serotype (14 cases) followed by serotype 19A (4 cases). Serotype 19A is not included in PCV7 or the 10-valent pneumococcal conjugate vaccine. Of note, macrolide resistance was relatively common in those cases and occurred in more than a third of isolates.

## Discussion

This study presents data on the serotype distribution of pneumococcal isolates from children and adults with spontaneously draining otitis media in Germany. The analysis included 512 cases, with 67.0% occurring in children aged  $< 5$  years. The results showed a relatively high rate of serotype 19F infections (21.5%), which is in accordance with the serotype distribution found in recent clinical studies and postlicensure surveillance of AOM in children in Finland [6], the Czech-Republic [27], and the USA [28]. However, some differences in serotype distribution, particularly regarding serotype 23F infections, were noted in the German data compared with distribution data from other countries.

A 2002 retrospective study, for example, analyzed nine geographically diverse data sets comprising pneumococcal isolates from MEF samples collected from children with AOM [28]. Samples were collected between 1994 and 2000 from 3,232 children in the USA, Argentina, Finland, France, Greece, Israel, and several Eastern European countries. The results showed that the most common serotypes in each data set and age group tended to be the same, despite variations in location, data-set design, and antibiotic resistance. Serotypes 23F, 19F, and 14 were most prominent, each comprising about 13% to 16% of the overall data set [28]. Serotypes 6B, 6A, 19A, and 9V were less common, each comprising about 5%

1 to 10% of all data sets. Serotypes 1, 5, and 7 contributed little (<2%) to overall pneumococcal  
2 AOM. Serotype 3 represented about 4% of the overall serotypes, and was most prominent in  
3 the youngest (<6 months) and oldest ( $\geq 60$  months) age groups (approximately 5.8% and  
4 21.5% of all isolates, respectively) [28].  
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9 In contrast to these observations, our analysis of data from German children and  
10 adults showed a lower rate of serotype 23F infections (10.0%) and a higher rate of serotype 3  
11 infections (13.9%). Globally, serotype 3 has become an increasingly significant MEF  
12 pathogen in children [10]. In German children aged <5 years, serotype 3 was found in 8.7%  
13 of cases. The coverage for the serotypes included in PCV7 (recommended for general use in  
14 children aged <2 years in Germany) was 60.3%, which was lower than the serotype coverage  
15 previously reported for IPD in Germany [18]. The inclusion of serotypes 1, 5, and 7F, which  
16 are in the 10-valent pneumococcal conjugate vaccine, increases the coverage by 3.3% to  
17 63.6%. The investigational 13-valent vaccine, which includes serotypes 3, 6A, and 19A in  
18 addition to the 10-valent vaccine serotypes, increases the coverage to 85.4%, mainly due to  
19 the inclusion of serotypes 3 and 19A (Figure 2).  
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36 Interestingly, we found a relatively high rate of reduced penicillin susceptibility  
37 (11.0%) in the present study. This rate was higher than that previously reported with invasive  
38 disease in German children [18]. In addition, we found a high rate of macrolide resistance  
39 (22.4%), in accordance with rates reported for IPD in children in Germany [18, 19]. These  
40 high resistance rates may reflect the complexity of many of the cases, which included otitis  
41 media therapy failures.  
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51 Our study has some limitations. First, it covers a long period of time, and the power is  
52 low. Admittedly, more patients and data would have been useful for our analysis—  
53 unfortunately we had no control over the number of the study population and were forced to  
54 rely only on the AOM serotype data available for Germany at the time of the study. A second  
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limitation is the fact that microbiological diagnosis is not done on a routine basis in Germany. Consequently, the incidence of AOM in Germany is probably under-reported, because only a portion of the thousands of children who contract AOM in Germany each year are tested. Mild IPD may be under-diagnosed in several European countries, because blood cultures are not usually ordered for outpatients, who may be treated with no documentation of their febrile episodes. Blood cultures may not be ordered for inpatients with fever without focus or with pneumonia [29]. Lastly, pneumococcal isolates used in our study were identified with standard microbiology methods. Use of more specific techniques, such as polymerase chain reaction (PCR), would have improved identification of otitis media-associated bacteria.

Despite these limitations, our retrospective analysis of pneumococcal strains gathered the data needed to provide a rough estimate of the pneumococcal serotypes that cause otitis media associated with spontaneous drainage in Germany. This information will be invaluable when planning vaccination strategies to protect against otitis media.

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**Conflicts of Interest** Dr Reinert is an employee of Pfizer Inc. Dr van der Linden has been a member of advisory boards for Wyeth and GlaxoSmithKline, and has received invitations to scientific conferences from Wyeth and GlaxoSmithKline.

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**Table 1** Sources of pneumococcal isolates from children with pneumococcal otitis media in

Germany

<b>Specimen</b>	<b>Number (%)</b>
Blood	24 (4.7)
Cerebrospinal fluid	33 (6.4)
Ear (tympanocentesis)	8 (1.6)
Mastoid	3 (0.6)
Pus middle ear	13 (2.5)
Swab ear	431 (84.2)
<b>Total</b>	<b>512 (100)</b>

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**Table 2** Coverage of the 7-valent, 10-valent, and investigational 13-valent pneumococcal conjugate vaccines in pneumococcal acute otitis media with ruptured tympanic membrane or sepsis isolates in Germany

Age Group	Vaccine formulation			Total
	7-valent	10-valent	13-valent	
<5 years ( <i>n</i> , %)	207 (60.3)	218 (63.6)	293 (85.4)	343 (100)
≥5 years ( <i>n</i> , %)	71 (42.0)	90 (53.3)	140 (82.8)	169 (100)
All ages ( <i>n</i> , %)	278 (54.3)	308 (60.2)	433 (84.6)	512 (100)

**Table 3** Antibiotic resistance in *S. pneumoniae* isolated from patients with acute otitis media in Germany (*n*=465)

<b>Resistance</b>	<b>Penicillin G <i>n</i> (%)</b>	<b>Clarithromycin <i>n</i> (%)</b>
Susceptible	406 (89.0)	349 (76.5)
Intermediate	30 (6.6)	5 (1.1)
Resistant	20 (4.4)	102 (22.4)
<b>Total</b>	<b>456 (100)</b>	<b>456 (100)</b>

**Table 4** Characteristics of invasive pneumococcal disease in children with pneumococcal otitis media (otogenic sepsis or meningitis) in Germany ( $n=33$ )

Patients ( $n=33$ )			Susceptibility		
Age, Gender	Diagnosis (Isolate)	Serotype	E-myc	Pen G	
5 mo, ND	Otitis perforans (B)	33A	S	S	
6 mo, M	Mastoiditis (B)	23F	S	S	
2 y, F	Meningitis, mastoiditis (CSF)	24F	S	S	
9 mo, F	ND (B)	19A	R	S	
3 y, M	Pneumonia, convulsion (B)	19A	R	S	
4 mo, M	Meningitis (CSF)	19A	ND	ND	
9 mo, F	Meningitis, mastoiditis (CSF)	19A	S	S	
1 y, F	ND (B)	19F	S	S	
3 y, M	ND (B)	19F	S	I	
1 y, M	Sepsis (B)	18C	S	S	
2 y, M	Meningitis (CSF)	18C	S	S	
1 y, F	ND (B)	14	R	S	
2 y, F	Pharyngitis (B)	14	R	S	
2 y, F	Pharyngitis (B)	14	R	S	
1 y, F	Pneumonia, coxitis (B)	14	R	S	
2 y, F	High fever (B)	14	R	S	
1 y, F	Sepsis (B)	14	R	S	
1 y, M	Mastoiditis (B)	14	R	S	
1 y, F	Meningitis (B)	14	R	S	
1 y, F	ND (B)	14	S	S	
1 y, F	Meningitis (CSF)	14	S	S	
1 y, M	Meningitis (CSF)	14	S	R	
7 mo, M	ND (CSF)	14	S	S	
1 y, M	Meningitis (CSF)	14	R	S	
1 y, M	Meningitis (CSF)	14	R	S	
1 y, M	Meningitis (CSF)	10A	S	S	
11 mo, M	Recurrent otitis (B)	9N	ND	ND	
4 y, ND	Chronic otitis (B)	7F	S	S	
11 mo, M	Meningitis (CSF)	7F	S	S	
1 y, M	Meningitis (CSF)	6A	S	S	
2 y, M	Sepsis, meningitis (B)	6B	S	S	
3 y, F	ND (B)	6B	S	S	
2 y, F	Meningitis, sepsis (CSF)	4	S	S	

*E-myc* erythromycin, *Pen G* penicillin G, *B* blood, *CSF* cerebrospinal fluid, *S* susceptible, *R* resistant, *I* intermediate, *ND* no data

**Fig. 1** Serotype Distribution for Pneumococcal OM Germany All Ages and <5 years

**Fig. 2** Coverage of different pneumococcal conjugate vaccine formulations in pneumococcal strains from otitis media in Germany (children aged <5 years). Red = serotypes included in the 7-valent vaccine; yellow = additional serotypes in the 10-valent vaccine; blue = additional serotypes in the investigational 13-valent vaccine; gray = other serotypes not included in any of the three vaccines.

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Figure 1  
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## Serotype Distribution for Pneumococcal OM Germany All Ages and <5 years

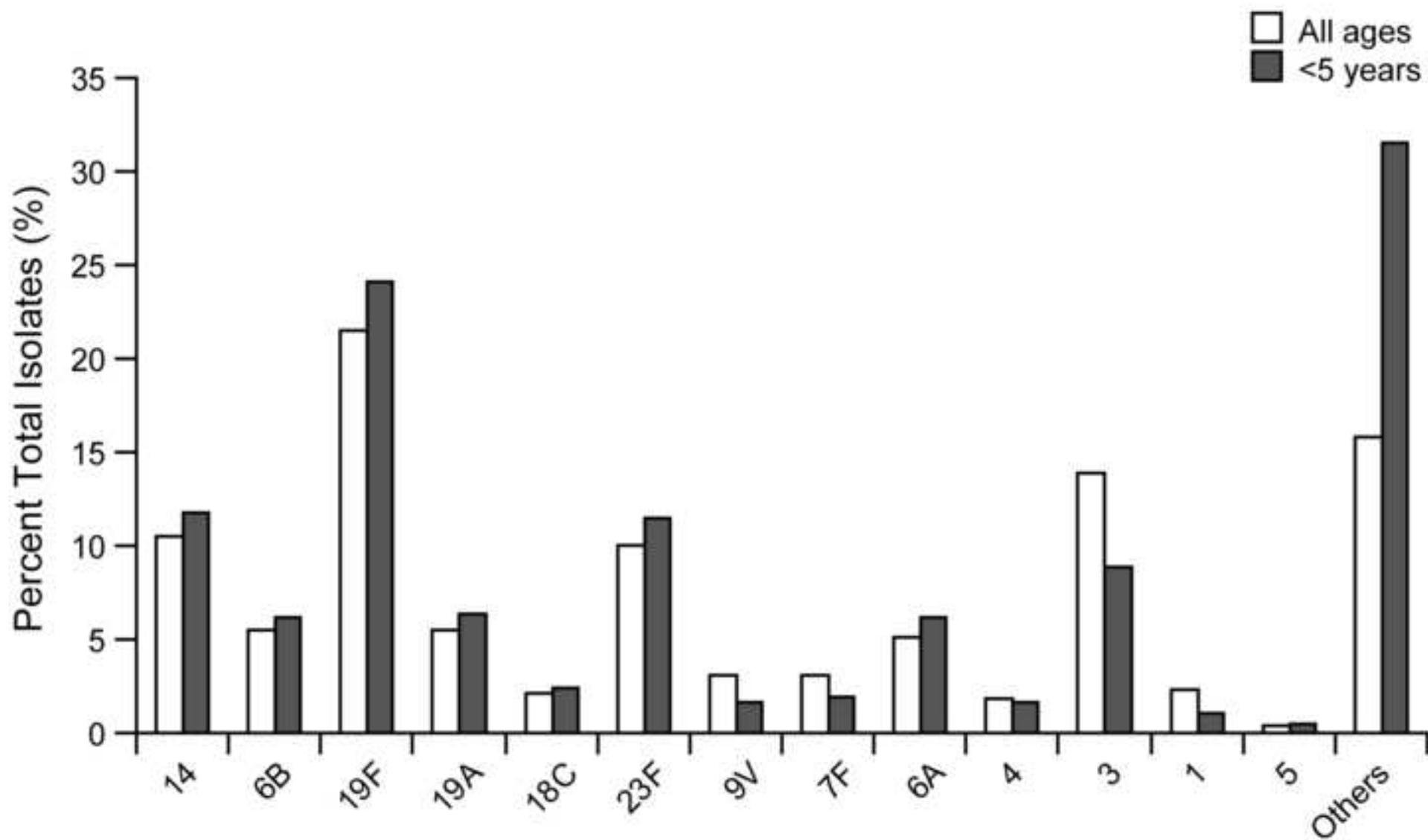


Figure 2

