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Invasive pneumococcal disease in adults in North-Rhine Westphalia, Germany, 2001–2003

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ABSTRACT

A population-based survey of invasive pneumococcal disease (IPD) was conducted among adults in North-Rhine Westphalia, Germany. The study included 202 of the 386 hospitals in the region, together with the 27 microbiological laboratories that submitted reports of IPD in these hospitals to the National Reference Centre for Streptococci. The reports of 16 laboratories were comprehensively reviewed. Most (95.8%) IPD isolates were susceptible to penicillin G, but 14.5% were resistant to clarithromycin. Serotypes 14 (15.6%), 3 (9.3%), 4 (7.1%) and 7F (7.9%) were the most common. The serotype coverage of the 23-valent pneumococcal polysaccharide vaccine was 80.8%. During 2001–2003, the annual incidence of IPD, after correcting for laboratory and hospital under-reporting, was 16.2/100 000 in individuals aged ≥65 years. In three university hospitals, blood cultures were obtained for only 37% of patients with community-acquired pneumonia, and fewer than one-third of such cultures were obtained in one hospital before antibiotics were prescribed, suggesting that the true incidence of IPD was closer to 50/100 000.

Keywords Clarithromycin, community-acquired pneumonia, penicillin G, resistance, serotypes, *Streptococcus pneumoniae*

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INTRODUCTION

Streptococcus pneumoniae is a leading cause of pneumonia, sepsis and meningitis among adults. The mortality rates associated with invasive pneumococcal disease (IPD) range from 5% to 35%, depending on the site of infection, patient's age and co-morbidity [1]. The possible prevention of pneumococcal disease with capsular polysaccharide vaccine has been studied for the past 90 years. Observational studies have shown that vaccination with the 23-valent pneumococcal polysaccharide vaccine prevents IPD in older adults [2]. In Germany, pneumococcal vaccination is recommended for elderly adults (aged ≥60 years) and for individuals with underlying high-risk conditions [3]. However, doubts remain about the value of pneumococcal vaccine, particularly its ability to provide long-term protection and to prevent cases of non-bacteraemic pneumococcal pneumonia [4–6].

Information regarding the annual incidence of IPD is essential for estimating the health and economic burden of pneumococcal disease, and for implementing and evaluating programmes for pneumococcal vaccination [7]. Such data are not available for many countries, including Germany. Furthermore, the future use of pneumococcal conjugate vaccines in elderly high-risk adults will require a detailed knowledge of the patterns of antibiotic resistance and serotype distribution of *S. pneumoniae* in this population [8]. The present study analysed the antibiotic resistance profiles and serotype distribution of isolates of *S. pneumoniae* from adults hospitalised with IPD in the German state of North-Rhine Westphalia. The incidence of IPD in different age groups, based on actual reports and after adjusting for factors contributing to the under-reporting of IPD, was calculated.

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MATERIALS AND METHODS

Study population

In Germany, the National Reference Centre for Streptococci (NRCS) has conducted nationwide prospective population- and laboratory-based surveillance of IPD for several years [8,9]. Surveillance for the current study focused on North-Rhine Westphalia, the largest federal state in Germany, with *c.* 18 million inhabitants. All 386 acute-care hospitals located in the state were invited to participate in the study. Of these, 202 (52.2%) agreed. The 27 microbiological laboratories serving these hospitals were identified, and all agreed to participate. A feasibility study was conducted between March 2001 and June 2001. The main study was conducted during the 2-year period from 1 July 2001 to 30 June 2003.

Hospitalised state residents aged ≥16 years were included in the study. A case of IPD was defined by the isolation of *S. pneumoniae* from a normally sterile site. Each case was considered to have occurred on the date the culture was obtained. NRCS staff communicated regularly with all microbiology laboratories serving the participating hospitals to ensure that standardised case report forms were completed. All suspected *S. pneumoniae* isolates were placed immediately in transport medium (Port-A-Cul; Difco, Detroit, MI, USA) and sent to the NRCS for species confirmation (optochin sensitivity and bile-solubility tests) and antimicrobial susceptibility testing.

Antibiotic sensitivity testing and serotyping

MICs of penicillin G, amoxycillin, cefotaxime, clarithromycin, clindamycin, tetracycline, gatifloxacin, ciprofloxacin and vancomycin were determined by the NCCLS microbroth dilution method [10] using Mueller–Hinton broth (Difco) supplemented with lysed horse blood (Oxoid, Wesel, Germany) 5% v/v. Plates were read after incubation at 35°C for 20–24 h in ambient air. *S. pneumoniae* ATCC 49619 was used as a reference strain. For determination of macrolide resistance phenotypes, disks of erythromycin (15 μg) and clindamycin (2 μg) (Oxoid) were placed 15–20 mm apart on Mueller–Hinton agar (BBL Microbiology Systems, Cockeysville, MD, USA) containing sheep blood (Oxoid) 5% v/v. Plates were inoculated with a swab dipped in a 0.5× McFarland standard bacterial suspension [11].

Pneumococcal isolates were serotyped by Neufeld's Quellung reaction using type- and factor-specific antisera (Statens Serum Institut, Copenhagen, Denmark).

Assessment of under-reporting of invasive pneumococcal disease by laboratories and hospitals

Surveillance for IPD can be biased by under-reporting of IPD cases by individual laboratories and hospitals. All 27 laboratories were asked to provide complete laboratory records of all cases of IPD, and 16 were able to do so. Data of all IPD isolates, sent by each of these 16 laboratories to the NRCS, were linked to the database of each laboratory's information system, thereby allowing the identification of cases of microbiologically confirmed IPD that were not reported to the NRCS. Using these data, a laboratory under-reporting factor (LUF) for each laboratory (the number of all IPD isolates identified by the laboratory divided by the number of isolates sent to the NRCS) and a mean LUF for all 16 laboratories were calculated. A hospital under-reporting factor (HUF) was also calculated by dividing the number of beds in all hospitals in the state (134 071) by the number of beds in the 202 participating hospitals (70 605).

Determining the incidence of invasive pneumococcal disease

The estimated annual incidence of IPD for specific age groups was calculated based on reports to the NRCS and population data provided by the 'Landesamt für Statistik', North-Rhine Westphalia (http://www.lds.nrw.de/statistik/landesdatenbank.html). An incidence rate corrected for laboratory and hospital under-reporting was also calculated for each age group by multiplying the NRCS-derived incidence rate by the LUF and the HUF.

Frequency of obtaining blood cultures and previous antibiotic therapy in patients with community-acquired pneumonia

For the year 2000, the frequency of obtaining blood cultures was determined for patients admitted to three university hospitals (Aachen, Düsseldorf and Cologne) with community-acquired pneumonia (CAP). In addition, the frequency of antibiotic treatment before blood cultures were obtained was determined for CAP patients in 2001 by a detailed analysis of patients' histories. All cases with a diagnosis of CAP (all diagnostic positions on the discharge summary) were identified retrospectively on the basis of ICD-10 codes (J13, J15.9, J18.0, J18.9). Cases were linked with data in the laboratory information system of each hospital's microbiological laboratory. Outcome data were obtained for all patients from the hospital discharge files of the individual hospitals.

RESULTS

Patient characteristics

During the 2-year study period, 647 IPD isolates were obtained from adults and submitted to the NRCS by the 27 microbiological laboratories. Of these, 491 (75.9%) were from blood, 36 (5.6%) from cerebrospinal fluid, 54 (8.3%) from bronchial lavage fluid, 30 (4.6%) from pleural punctures, and 36 (5.6%) from other normally sterile sites. Most isolates (404; 62.4% of cases) were obtained from patients aged ≥60 years, with 55.2% of all isolates being obtained from male patients. Clinical diagnoses were available for 404 of the 647 isolates, and 246 (60.6%) of these patients were diagnosed with bacteraemic pneumococcal pneumonia.

Antibiotic sensitivity

Among all IPD isolates, 95.8% were susceptible to penicillin G (MIC < 0.06 mg/L), 3.9% were penicillin-intermediate (MIC 0.1–1 mg/L), and only

Table 1. Antibiotic sensitivities of 647 pneumococcal isolates from adults with invasive pneumococcal disease in North-Rhine Westphalia, Germany, 2001–2003

	MIC range (mg/L)	MIC_{90} (mg/L)	% I	% R	NCCLS breakpoints (mg/L) I	NCCLS breakpoints (mg/L) R
Penicillin G	≤ 0.016–2	0.03	3.9	0.3	0.12–1	≥ 2
Amoxycillin	≤ 0.016–2	0.03	0.2	0.0	4	≥ 8
Cefotaxime[a]	≤ 0.016–2	0.016	0.8	0.1	2	≥ 4
Clarithromycin	≤ 0.06 to ≥32	4	0.6	14.5	0.5	≥ 1
Clindamycin	≤ 0.06 to ≥32	0.06	0.2	3.9	0.5	≥ 1
Telithromycin	≤ 0.016–0.5	0.06	0.0	0.0	2	≥ 4
Tetracycline	0.06 to ≥32	1.0	0.3	6.8	4	≥ 8
Gatifloxacin	≤ 0.016–2	0.25	0.2	0.0	2	≥ 4
Ciprofloxacin[b]	0.25–4	2.0	0.0	0.3	–	≥ 4
Vancomycin	0.06–1	0.5	0.0	0.0	–	–

I, intermediately-resistant; R, resistant.
[a]Breakpoints for cefotaxime (meningitis): 1 mg/L, ≥ 2 mg/L.
[b]Ciprofloxacin breakpoints have not been published by the NCCLS; a breakpoint of ≥ 4 mg/L was used [16,17].

0.3% were penicillin-resistant (MIC ≥ 2 mg/L) (Table 1). The combined rates of intermediate resistance and resistance to amoxycillin and cefotaxime were 0.2% and 0.9%, respectively. Overall, 7.1% of isolates had reduced susceptibility to tetracycline, 4.1% to clindamycin and 15.1% to clarithromycin. During the study period, an increase in macrolide resistance was observed (13.0% in year 1; 16.5% in year 2). Of the clarithromycin-non-susceptible isolates (n = 98), 25 and 73 showed the MLS_B and M phenotypes, respectively. Only 0.1% of isolates were gatifloxacin-intermediate, and all were susceptible to telithromycin and vancomycin (Table 1).

Serotype distribution and coverage by pneumococcal vaccines

The leading serotypes were serotypes 14 (15.6%), 3 (9.3%), 7F (7.9%) and 4 (7.1%) (Table 2). Serotype coverage by the 23-valent polysaccharide vaccine was 80.8% for all age groups and 82.1% for the group aged ≥65 years. Serotype coverages by the 7- and 11-valent conjugate vaccines were 47.4% and 64.1%, respectively.

Under-reporting of invasive pneumococcal disease by laboratories and hospitals

Of the 27 laboratories, 16 were able to provide information for all their IPD isolates (Table 3). These 16 laboratories submitted 476 (73.6%) of 647 isolates sent to the NRCS. However, according to information systems in these 16 laboratories, 884 cases fulfilled inclusion criteria for IPD, indicating that 408 (46.2%) of IPD isolates had not been sent to the NRCS. From this, a mean LUF was

Table 2. Serotype distribution of *Streptococcus pneumoniae* isolates from adults with invasive pneumococcal disease in North-Rhine Westphalia, Germany, 2001–2003

Rank	Serotype	Number	Percentage	Cumulative percentage[a]
1	14	101	15.6	15.6
2	3	60	9.3	24.9
3	4	46	7.1	32.0
4	7F	43	6.6	38.6
5	23F	38	5.9	44.5
6	1	33	5.1	49.6
7	9V	30	4.6	54.3
8	6A	29	4.5	58.7
9	8	24	3.7	62.4
10	19F	21	3.2	65.7
11	6B	21	3.2	68.9
12	12F	18	2.8	71.7
13	18C	14	2.2	73.9
14	11A	13	2.0	75.9
15	9N	13	2.0	77.9
16	22F	12	1.9	79.8
17	9A	12	1.9	81.6
18	10A	10	1.5	83.2
19	9L	10	1.5	84.7
20	24F	9	1.4	86.1
21	17F	7	1.1	87.2
22	19A	7	1.1	88.3
23	31	7	1.1	89.3
	Others[b]	67	10.4	99.7
	NT	2	0.3	100.0
	Total	647	100.0	

NT, non-typeable.
[a]Coverage of the 7-valent (11-valent) pneumococcal conjugate vaccine by age group: 16–35 years, 46.5% (67.4%); 35–65 years, 47.2% (62.4%); > 65 years, 47.8% (65.4%); all ages, 47.4% (64.2%). The 7-valent conjugate vaccine strains included serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. The 11-valent vaccine includes the 7-valent vaccine types plus additional serotypes 1, 3, 5 and 7F. Coverage of the 23-valent pneumococcal conjugate vaccine by age group: 16–35 years, 76.4%; 35–65 years, 80.1%; > 65 years, 82.1; all ages, 80.8%. Serotypes in the 23-valent polysaccharide include the 11-valent serotypes plus serotypes 2, 6A, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F and 33F.
[b]Others include the following types (no. of isolates): 35F (6); 5 (6); 16F (5); 20 (5); 38 (5); 33F (4); rough (4); 13 (3); 15A (3); 15B (3); 23A (3); 28A (3); 7C (3); 12A (2); 12B (2); 15C (2); 15F (1); 23B (1); 25F (1); 29 (1); 34 (1); 35C (1); 36 (1); and 37 (1).

Table 3. Under-reporting of invasive pneumococcal disease by laboratory-based surveillance in North-Rhine Westphalia, Germany, 2001–2003

Laboratory	No. of isolates actually obtained	No. of isolates sent to the NRCS	Laboratory under-reporting factor (LUF)
6	130	107	1.21
13	224	62	3.61
7	59	59	1.00
11	64	56	1.14
10	36	36	1.00
3	89	33	2.70
15	42	27	1.56
9	22	22	1.00
12	71	17	4.18
2	29	13	2.23
16	24	12	2.00
4	71	9	7.89
8	9	9	1.00
1	6	6	1.00
14	6	6	1.00
5	2	2	1.00
Total	884	476	1.86

LUF, the number of isolates actually obtained divided by the number of isolates reported to the NRCS.

Table 4. Estimated incidence of invasive pneumococcal disease in North-Rhine Westphalia, Germany, 2001–2003

Age group (years)	Mean no. of cases/year	Population (× 100 000)[a]	Estimated incidence based on reports to the NCRS (/100 000)	Estimated incidence, adjusted for LUF and HUF[b]
> 16–44	51	71.4	0.7	2.5
45–64	111	46.1	2.4	8.5
65–74	74.5	10.9	6.8	24.1
75–84	55	18.8	2.9	10.3
≥ 85	21	3.0	7.1	25.1
≥ 65	150.5	32.9	4.6	16.2
Total	463	150.4	3.079	10.87

[a]Landesamt für Statistik, North-Rhine Westphalia (http://www.lds.nrw.de/statistik/landesdatenbank.html).
[b]The adjusted estimated incidence was calculated by multiplying the number of cases by the laboratory under-reporting factor (LUF) and the hospital under-reporting factor (HUF). See text for details.

calculated of 1.86 (Table 3). It was assumed that the same LUF would apply to the 11 other laboratories. The HUF (see Methods) was 1.90.

Incidence of invasive pneumococcal disease

The estimated annual incidences of IPD are shown in Table 4. For individuals aged ≥ 65 years, the estimated incidence, based on reports to the NRCS, was 4.6/100 000. After correcting for laboratory and hospital under-reporting, the estimated incidence in elderly individuals was 16.2/100 000.

Frequency of obtaining blood cultures and of previous antibiotic therapy in patients with community-acquired pneumonia

During 2000, 1254 patients with CAP were hospitalised in three participating hospitals (Table 5). Blood cultures were obtained for *c*. 50% of CAP patients in two of these hospitals, but for only 14.8% of CAP patients in the third hospital. Overall, blood cultures were obtained for 37.0% of CAP patients, but only 11 (2.4%) blood cultures were positive for *S. pneumoniae*.

Table 6. Relationship between blood cultures and previous antibiotic treatment in 112 patients hospitalised with community-acquired pneumonia in North-Rhine Westphalia, Germany, 2001

	Previous antibiotic treatment (%)		
	Yes	No	Total
Blood culture obtained (%)			
Yes	10.7	30.4	41.1
No	13.4	45.5	58.9
Total	24.1	75.9	100.0

In addition, the history of previous antibiotic treatment was evaluated in one university hospital for 112 randomly selected CAP patients. Of these, blood cultures were obtained for 46 (41.1%) patients, but 12 (26.1%) were already being treated with antibiotics when the cultures were obtained (Table 6). Thus, only 34 (30.4%) of the 112 CAP patients had cultures taken that could have confirmed the presence or absence of bacteraemic pneumococcal pneumonia.

DISCUSSION

Surveillance of IPD has been ongoing in Germany since the early 1990s, but most reports have focused on infections in children [9,12,13]. The present study was undertaken to gain an understanding of the epidemiology of IPD in adults, including the antibiotic susceptibility of invasive isolates, and the serotype distribution and incidence of invasive disease in specific age groups.

Previous reports from Germany have documented a relatively low level of resistance to β-lactams among *S. pneumoniae* isolates, and a very low frequency of penicillin-resistant strains. These findings were confirmed in the current study; 3.9% of isolates were penicillin-resistant or -intermediate, and only 0.3% were penicillin-resistant. No significant differences were observed between the levels of β-lactam resistance in *S. pneumoniae*

Table 5. Blood culture rates for 1254 adults with community-acquired pneumonia (CAP) in three university hospitals in North-Rhine Westphalia, Germany, 2000

Hospital	Cases of CAP	Cases in which a blood culture was obtained	% of all CAP patients	Cases with a positive blood culture	% of all CAP patients	Cases with *Streptococcus pneumoniae* in blood culture	% of all CAP patients	Case fatality rate (%)
1[a]	302	168	55.6	53	17.5	5	1.7	15.6
2	494	228	46.2	57	11.5	4	0.8	14.2
3	458	68	14.8	42	9.2	2	0.4	9.2
Total	1254	464	37.0	152	12.1	11	1.0	13.0

[a]In this university hospital, the rate of previous antibiotic treatment was determined for 112 of the 168 patients from whom cultures were obtained.

isolates obtained from adults and those reported in earlier studies of children. In a separate population-based study of IPD in German children, von Kries *et al.* [9] reported that 3.3% of invasive isolates had intermediate susceptibility to penicillin, but that none was resistant.

In contrast to these low levels of resistance to β-lactams, the present study found that levels of macrolide resistance among pneumococci were increasing. More than 15% of invasive isolates from adults were clarithromycin-resistant, confirming findings of earlier studies in adults [12] and children [9]. Moreover, a relatively high rate of M phenotype strains among macrolide-resistant isolates in Germany has been reported [14]. The increase in macrolide resistance in Germany is worrisome and underscores the need to add pneumococcal conjugate vaccine to the German childhood vaccination programme. In the USA, macrolide resistance among isolates causing invasive pneumococcal disease increased steadily from 4.5/100 000 in 1994 to 9.3/100 000 in 1999. Following the introduction of childhood vaccination in 2001, this frequency fell to 2.9/100 000 in 2002 [15]. This experience indicates that vaccination with pneumococcal conjugate vaccine can be an effective strategy for reducing antibiotic resistance in a community.

The level of fluoroquinolone resistance detected (0.3%) was significantly lower than the levels reported from Canada [16] and Spain [17]. Newer fluoroquinolones with greater potency against *S. pneumoniae* (e.g., levofloxacin and moxifloxacin) have been licensed recently in Europe. Because of the emergence of antimicrobial resistance in pneumococci [18], these agents are now recommended for the empirical treatment of pneumonia in adults when resistance is suspected [19]. In several countries, fluoroquinolones are also recommended for initial empirical therapy of selected outpatients with community-acquired respiratory tract infections (e.g., patients with acute exacerbations of chronic bronchitis) [19,20]. Pneumococcal resistance to quinolones is caused by mutations in either *parC* or *gyrA*, or both [21]. Strains become fully fluoroquinolone-resistant following a second mutation in the other target gene (either *gyrA* or *parC*). Some strains with ciprofloxacin MICs ≥ 4 mg/L and mutations in the quinolone resistance-determining regions remain susceptible to newer fluoroquinolones, but the therapeutic value of newer quinolones for infections caused by these strains needs further investigation.

The level of tetracycline resistance (6.8%) was lower than the levels observed in the early 1990s [22]. Marked differences in antibiotic susceptibility among pneumococcal isolates have been reported from several European countries [23]. Among the possible responsible factors, different levels of antibiotic consumption may be among the most important [24,25]. Goossens *et al.* [26] reported higher rates of antibiotic resistance in southern and eastern Europe than in northern Europe, probably caused by the higher consumption of antibiotics in southern and eastern Europe.

Serotypes 14, 3, 4, 7F, 23F and 1 were the leading serotypes responsible for IPD in adults. In other European countries, the serotype distribution varies, but overall the coverage provided by the 23-valent pneumococcal polysaccharide vaccine is relatively stable, ranging from 80% to ≥ 90% [2]. It is notable that a relatively high rate of serotype 1 infections was found, which confirms the findings of other investigators [27].

An evaluation of temporal trends in the serogroup distribution of invasive isolates obtained in the USA between 1928 and 1998 revealed that the proportion of infections caused by serogroups included in the 7-valent pneumococcal conjugate vaccine increased from 15% to 59% during this period [28]. In contrast, the proportion of infections caused by the 'epidemic' serogroups (1, 2, 3 and 5) decreased from 71% to 7% in adults, and from 18% to 2% in children. Socio-economic factors, such as crowded living conditions, probably promoted outbreaks of epidemic serogroup disease, but these factors have become less common, favouring the transmission of 'paediatric' serotypes, rather than epidemic serogroups, from children to adults [28]. The present findings from Germany are compatible with this hypothesis. The efficacy of the 23-valent pneumococcal polysaccharide vaccine has not been demonstrated for non-invasive pneumococcal disease in elderly and high-risk adults [2,6], but it might be useful in this group. In contrast, the current 7-valent conjugate vaccine might be inadequate, as only 47.4% of IPD isolates were covered by the 7-valent vaccine. The relatively low coverage of adult serotypes by the 7-valent vaccine has also been reported from other countries [8].

Epidemiological studies based solely on laboratory surveillance can be biased because of under-

reporting. Thus, for every case of IPD reported to the NRCS, almost one additional case went unreported (mean LUF = 1.86). This finding is similar to that of an earlier nationwide study of IPD in children that used a capture–recapture method to analyse laboratory- and hospital-based surveillance data [9]. Laboratory-based surveillance failed to detect *c.* 50% of these IPD cases. The present study is the first to attempt to estimate the incidence of IPD for adults in Germany. As in other countries, IPD is relatively infrequent among younger adults. After correction for laboratory and hospital under-reporting, the incidence was 0.9–4.0/100 000 in individuals aged < 50 years. Above this age, the incidence increased substantially to 16.2/100 000 in individuals aged ≥ 65 years. Similar findings have been reported for this age group from England and Wales (21/100 000), France (18/100 000) and Sweden (27/100 000), although much higher rates have been reported from Denmark (64/100 000), The Netherlands (63/100 000), Norway (62/100 000) and Spain (57/100 000) [2].

The large variations (more than three-fold) in the reported incidence of IPD between different countries, and even greater differences between regions within individual countries, do not seem to be related to real variations in the magnitude of disease occurrence, but rather to differences in surveillance systems and the ascertainment of individual cases [2]. In the present study, blood cultures were obtained from only 37% of CAP patients in three university hospitals, and, in one hospital, less than one-third of all CAP patients had a blood culture taken before being treated with antibiotics, meaning that only in this group could the presence or absence of bacteraemic pneumococcal pneumonia be determined accurately. It is unlikely that the other two hospitals differed in this respect. The failure to obtain blood cultures for most patients hospitalised with CAP has been reported previously in the UK [2]. In addition, a study in Italy [29] found that incidence rates for invasive pneumococcal disease in individuals aged ≥ 65 years were 5.7 and 0.2/100 000, respectively, but that only 27% and 7%, respectively, of hospitalised patients with pneumonia had either blood or cerebrospinal fluid cultures taken. Thus, it seems to be a common finding that only about one-third of CAP patients have a blood culture taken before the use of antibiotics.

A retrospective study in Germany found that blood cultures were taken frequently for children with sepsis (96%) and meningitis (95%), but less frequently for those with pneumonia (49%) and fever without focus (48%) [30]. In addition, a prospective study of adults hospitalised with CAP in five centres in Canada, the USA, the UK, Spain and Sweden showed that previous antibiotic treatment and rates of obtaining blood cultures for CAP patients varied considerably among countries, and that the incidence of IPD could be under-reported by a factor of at least two [31]. Blood culture sampling rates might be too low to provide a sensitive indication of the incidence of IPD in children, perhaps more so in Europe than in the USA [30,32], and the same seems to be true for older adults. This may help to explain the large differences between the reported incidence of IPD among adults in the USA and those reported in several European countries.

In conclusion, the present study revealed that the incidence of IPD for individuals aged ≥ 65 years, corrected for laboratory and hospital under-reporting, was 16.2/100 000. Bacteraemic pneumococcal pneumonia accounts for *c.* 80–90% of all invasive pneumococcal disease in most case series [2], but only 60.6% of the isolates sent to the NRCS listed pneumonia as the clinical diagnosis. In addition, blood cultures were obtained from only about one-third of CAP patients and, in many cases, were probably obtained after, rather than before, antibiotic treatment was started. These findings indicate strongly that IPD was under-reported, and that the true incidence of IPD in this age group was probably close to 50/100 000 [2]. The level of β-lactam resistance among IPD isolates in German adults was still low, but increasing resistance to macrolides is of concern. As in other countries, the serotype coverage by the 23-valent vaccine for IPD in adults is high. Correcting for under-reporting, the incidence of IPD in elderly adults is comparable to that in many other countries. These findings provide a solid evidence base for current pneumococcal vaccination recommendations for adults in Germany.

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