BMJ Open

Incidence of all-cause and vaccine-preventable, radiologically confirmed community-acquired pneumonia in hospitalised adults in Germany: a multicentre surveillance study (2021–2023)

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To cite: Theilacker C, Hagel S, Ankert J, *et al*. Incidence of all-cause and vaccine-preventable, radiologically confirmed community-acquired pneumonia in hospitalised adults in Germany: a multicentre surveillance study (2021–2023). *BMJ Open* 2026;**16**:e109621. doi:10.1136/bmjopen-2025-109621

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-109621).

Received 19 August 2025
Accepted 05 February 2026

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ABSTRACT

Objectives Accurate estimates of the burden of vaccine-preventable community-acquired pneumonia (CAP) hospitalisations both overall and due to the most frequent and vaccine-preventable pathogens are needed to inform the use of respiratory vaccines in adults.

Design and setting This was a prospective, population-based CAP surveillance study at three hospitals in Germany. All patients admitted with clinically suspected CAP were tested for *Streptococcus pneumoniae* using urine antigen tests and for respiratory syncytial virus (RSV), influenza virus and SARS-CoV-2 using multiplex PCR from nasopharyngeal swabs. Incidence rate calculations for all-cause CAP were based on eligible patients, regardless of enrolment status.

Participants Individuals admitted to study hospitals within the surveillance period with suspected or confirmed diagnosis of pneumonia who provided informed consent.

Outcome measures Radiologically confirmed (RAD) CAP.

Results Active surveillance between 1 January 2021 and 30 June 2023 identified at the three study sites 4319 adults with RAD-CAP that met eligibility criteria, of which 1479 (34.2%) were enrolled and included in the analysis for pathogen distribution. The main reason for non-enrolment was the inability to provide informed consent. Incidence estimates were based on 1254 study-eligible individuals admitted at the largest study site. SARS-CoV-2, *S. pneumoniae*, RSV or influenza were identified in 36.5%, 9.1%, 3.7% and 1.8% of patients with RAD-CAP, respectively. Serotypes included in the 20-valent pneumococcal conjugate vaccine were detected in 6.9% of RAD-CAP and 76.0% of pneumococcal CAP. The overall adjusted annual incidence of all-cause RAD-CAP over the study period was 490/100 000 (95% CI 461 to 521). The incidence of pneumococcal and RSV-related RAD-CAP increased 8.6-fold and 10.0-fold over the study period, resulting in an incidence of 60/100 000 (95% CI 45 to 75) and 30/100 000 (95% CI 19 to 41) in 2022/2023, respectively, while SARS-CoV-2 related RAD-CAP declined by 70% to 97/100 000 (95% CI 78 to 116).

Conclusions Active pneumonia surveillance reported a high burden of RAD-CAP hospitalisations in Germany, especially among older adults. The resurgence of CAP due to RSV, *S. pneumoniae* or influenza, alongside maintained activity of SARS-CoV-2, was associated with an overall increase of RAD-CAP among adults.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We employed active surveillance using broad screening criteria to ensure near complete capture of hospitalised community-acquired pneumonia (CAP) cases.
⇒ Collection of minimal data on non-enrolled study-eligible patients and high microbiological testing rates among enrolled patients provided a more complete description of CAP aetiology.
⇒ As microbiological testing was limited to enrolled patients, who were a younger and healthier subset of hospitalised patients with CAP, the prevalence of some pathogens disproportionally affecting older or more severely ill individuals (eg, respiratory syncytial virus) may have been underestimated.
⇒ CAP incidence estimates from study sites and a study period that partially overlapped with pandemic-related, non-pharmaceutical measures may not be fully generalisable.

BACKGROUND

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality globally. Combined with other lower respiratory tract infections (LRTI), CAP ranks as the fifth leading cause of disability-adjusted life years across all ages globally[1] and accounts annually for 19 640 deaths in adults in Germany.[2] *Streptococcus pneumoniae* is the most common bacterial pathogen in CAP,

and influenza virus, SARS-CoV-2 and respiratory syncytial virus (RSV) are the most frequent viral causes.[3] With the emergence of SARS-CoV-2 in late 2019 and the following COVID-19 pandemic, the epidemiology of LRTI has changed substantially, and while SARS-CoV-2 continues to circulate, pre-pandemic aetiologies have resurged in many countries.[4]

Few studies on CAP incidence in Germany are available,[5–10] and only four studies have provided estimates for the past 10 years.[5 7 8 10] Of those, only one reported pneumonia incidence among hospitalised patients and was conducted well before the COVID-19 pandemic and ensuing changes to the epidemiology of respiratory infection.[10 11] Moreover, all recent estimates were based on case identification using discharge diagnosis codes from administrative data. This has several limitations, including low testing rates for CAP pathogens in routine clinical care, inadequate specimen collection, insensitive diagnostic tests and underutilisation of pathogen-specific International Classification of Diseases, 10th Revision (ICD-10) codes, that may substantially underestimate the pneumonia burden.[12] Lack of data hampers rational decision-making regarding use of newly developed vaccines to prevent LRTI in adults, including higher valency pneumococcal conjugate vaccines (PCVs; PCV15, PCV20, PCV21), COVID-19 vaccines, RSV vaccines and improved formulations of influenza vaccines.

The objective of this study was to describe among adults living in Germany the burden of all-cause radiologically confirmed CAP (RAD-CAP) overall and due to the most frequent and vaccine-preventable pathogens, namely *S. pneumoniae*, SARS-CoV-2, RSV and influenza. We conducted a prospective, multicentre, active surveillance study in three hospitals in the federal state of Thuringia (Germany) and aimed to provide accurate estimates of the incidence rate (IR) of CAP between 2021 and 2023.

MATERIALS AND METHODS

Study design and setting

This was an active surveillance study of adults with hospitalised RAD-CAP conducted at three hospitals in Thuringia (Germany) between 1 January 2021 and 30 June 2023.

Participants

All patients admitted to hospital were screened for CAP using ICD-10 admission codes, radiological reports and clinical microbiology results regardless of admission pathway. Those with a diagnosis or clinical suspicion of pneumonia (or their legally acceptable representatives) were approached for informed consent if hospitalised for <96 hours. Further details and inclusion/exclusion criteria are presented in online supplemental methods.

Laboratory methods

Nasopharyngeal (NP) or mid-turbinate swabs and urine samples were collected from all participants on the day of enrolment. Swabs were tested by multiplex PCR for nine respiratory viruses in local microbiology laboratories (for details see online supplemental methods). NP/mid-turbinate swabs for SARS-CoV-2 PCR from participants were obtained either as part of standard of care (SoC) or as a study procedure if routine testing was unavailable. Urine samples were tested with the commercially available pneumococcal urinary antigen test ((PUAT), BinaxNOW *S. pneumoniae*) and the proprietary serotype-specific urinary antigen detection (UAD) tests UAD1 and UAD2, which detect all serotypes included in PCV13, PCV15, PCV20 and 23-valent pneumococcal polysaccharide vaccine (PPV23).[13 14] SoC culture isolates of *S. pneumoniae* from sterile sites or the lower respiratory tract specimens were serotyped by a reference laboratory for streptococci as described elsewhere.[15]

Variables collected

Demographic variables, medical history and chronic comorbidities were collected by patient interview and medical chart review and used to derive pneumococcal disease risk category according to established definitions (for details see online supplemental methods).[16 17] Vaccination status was extracted from vaccination certificates or medical files, and if unavailable from these sources from patient interview. In addition, the Pneumonia Severity Index score[18] and the Confusion, Respiratory Rate, Blood Pressure-65 score (CRB-65 score)[19] at the time of hospital admission, admission chest imaging results, SoC microbiology testing results, need for intensive care unit (ICU) and ventilation support, the duration of hospital stay and in-hospital mortality were recorded. Final study diagnosis of RAD-CAP was confirmed at time of discharge by study investigators after review of all available clinical data.

Pneumonia surveillance

The study staff at Jena University Hospital (JUH) maintained active surveillance with near complete capture of study eligible cases for the full study period. For the other two study hospitals, case capture was incomplete due to the impact of the COVID-19 pandemic on the study activities. As a result, all three study hospitals contributed to the reported pathogen detections among enrolled participants, while incidence estimates are only based on case numbers and base population of the largest study hospital which provided complete case capture (online supplemental figure 1).

Anonymised, minimal data (age group, sex, risk group status, CRB-65 score, ICU admission, length of hospital stay, in-hospital death) were collected for all admitted patients meeting eligibility criteria regardless of enrolment status. A surveillance audit at JUH ascertained the completeness of the capture of eligible patients by the study screening process. Patients were considered positive for *S. pneumoniae* if at least one pneumococcal test was positive (sterile-site culture, respiratory culture, PUAT, UAD1 or UAD2) (for details see online supplemental methods).

Estimation of incidence rates and statistical analysis

All analyses reported here were restricted to patients with RAD-CAP with an onset no later than 48 hours after hospital admission. RAD-CAP IRs are reported by epidemiological year (July to June), and over the surveillance period of 24 months of surveillance between July 2021 and June 2023, to avoid a mid-peak split during the COVID-19 pandemic, the first 6 months of surveillance (January–June 2021) were excluded from incidence estimates.

For the calculation of CAP IRs, the catchment population of JUH of 109 149 adults aged ≥18 years was adjusted to account for catchment area residents seeking hospital care in other hospitals according to a market share analysis.[20] Details on the market share analysis are provided in the online supplemental methods. All eligible patients regardless of enrolment status, contributed as cases for the incidence calculation. Assuming similar probabilities for a positive test result among tested and not tested individuals as well between sites, we calculated pathogen-specific IRs by multiplying age-group specific incidence of all-cause pneumonia of JUH catchment area residents by the proportion of each pathogen detected among patients with a valid test result within age groups (18–64 years, 65+ years) from all three study sites. IRs are expressed as the number of cases per 100 000 adults aged ≥18 years and 95% CIs were calculated based on Poisson distribution. Statistical analyses were conducted in SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Study population and disease characteristics

Across the duration of the study, a total of 4705 patients with CAP meeting study eligibility criteria were identified at all three study sites, with 2150/4705 (45.7%) admitted at JUH. Of those, 1577/4705 (33.4%) and 719/2150 (33.4%) were enrolled at the combined study sites and JUH, respectively. When compared with CAP cases identified by manual chart review in a random sample of all hospital admissions at JHU, the study surveillance captured 90% of all admitted CAP cases. The most common reason for non-enrolment was the inability to provide informed consent (online supplemental figure 1). Of the enrolled patients, 1479/1557 (95.0%) had RAD-CAP and 11/1557 (0.7%) had clinically diagnosed CAP not confirmed by radiology. Compared with enrolled patients, non-enrolled patients were older, more frequently comorbid, had higher CRB-65 scores, were more often admitted to the ICU and had a higher in-hospital case fatality rate (online supplemental tables 1 and 6). There were also some differences in patient baseline characteristics by study site, with cases admitted at JUH being more severe (online supplemental table 2).

The median age of enrolled study patients from all sites was 70 years, and 59.5% (880/1479) were male (table 1). 12.8% (189/1479) and 7.7% (114/1479) of patients needed intensive care and mechanical ventilation support, respectively. Patients were hospitalised for a median period of 9 days and 7.2% (107/1479) died during the hospital stay. Further details of the presentation and complications of RAD-CAP are summarised in online supplemental tables 3 and 5.

CAP pathogens

Of the study participants, 70.2% (1038/1479) had SoC blood culture results available and 81.4% (1204/1479), 92.9% (1374/1479) and 96.6% (1428/1479) had valid results for UAD/PUAT assays, multiplex respiratory pathogen PCR and SARS-CoV-2 PCR (online supplemental figure 1). The most common respiratory pathogens isolated were SARS-CoV-2 (36.5%), *S. pneumoniae* (9.1%), rhinovirus (5.4%), RSV (3.7%), parainfluenza virus (3.3%) and human metapneumovirus (2.4%) (table 2). RAD-CAP associated with influenza A or B was infrequent during the study period (1.8%). Results from SoC bacterial culture testing are summarised in online supplemental table 4 and per-protocol testing results using age group definitions of Germany's Robert-Koch Institute (RKI) are shown in online supplemental table 8.

The prevalence of vaccine-preventable CAP pathogens changed substantially over the study period (figure 1). SARS-CoV-2 was the predominant pathogen during the early study period and declined thereafter but still accounted for 18% (83/451) of cases in 2022/2023. *S. pneumoniae*, RSV or influenza virus was almost absent as a cause of RAD-CAP during the first 6 months of 2021 but increased thereafter. In 2022/2023, *S. pneumoniae*, RSV or influenza virus was isolated from 11.6% (51/439), 5.6% (25/445) and 4.0% (18/447) of cases, respectively.

Of the 96 cases of pneumococcal CAP between July 2021 and June 2023, the most frequent serotypes were 3 (24/96 cases, 25.0%), 1 (8/96 cases, 8.3%), 8 (8/96 cases, 8.3%), 6A/C (6/96 cases, 6.3%), 11A (5/96 cases, 5.2%) and 22F (5/96 cases, 5.2%) (table 3). Among RAD-CAP cases due to any causes, PCV13, PCV15 and PCV20 serotypes were detected in 5.1% (19/369), 5.7% (21/369) and 8.1% (30/369) in adults aged 18–64 years and in 4.4% (30/687), 4.5% (31/687) and 6.3% (43/687) in adults ≥65 years, respectively. The proportion of RAD-CAP caused by serotype included in PCVs increased in 2022/2023 and serotypes included in PCV13, PCV15 and PCV20 accounted for 6.8% (30/439), 7.5% (33/439) and 9.8% (43/439) of RAD-CAP (figure 2) and 58.8% (30/51), 64.7% (33/51) and 84.3% (43/51) of pneumococcal CAP in 2022/2023. Pneumococcal serotype distribution and pneumococcal vaccine coverage in RAD-CAP using age group definitions of the RKI are shown in online supplemental tables 7 and 9.

Incidence rate of RAD-CAP

Of the 109 149 catchment area residents aged ≥18 years,[21] 97% of hospital care was sought at JUH according to the market share analysis performed by the study team, resulting in an adjusted base population of 105 547 individuals. The denominator-adjusted annual incidence of all-cause RAD-CAP between 2021/2022 and 2022/2023

Table 1 Clinical characteristics of study population January 2021 to June 2023

	≥18 years (N*=1479)	18–64 years (N*=532)	≥65 years (N*=947)
	n (%)	n (%)	n (%)
Age (median, IQR)	70 (60–81)	56 (47–61)	78 (71–83)
Age category (years)			
18–49 years	151 (10.2)	151 (28.4)	0
50–59 years	381 (25.8)	215 (40.4)	0
60–74 years	362 (24.5)	166 (31.2)	362 (38.2)
≥75 years	585 (39.6)	0	585 (61.8)
Sex			
Female	599 (40.5)	196 (36.8)	403 (42.6)
Male	880 (59.5)	336 (63.2)	544 (57.4)
White race	1463 (98.9)	519 (97.6)	944 (99.7)
High-risk condition†	664 (44.9)	167 (31.4)	497 (52.5)
Immunosuppression therapy	243 (16.4)	93 (17.5)	150 (15.8)
Immunodeficiency	31 (2.1)	16 (3.0)	15 (1.6)
HIV/AIDS	2 (0.1)	2 (0.4)	0
Solid tumour	339 (22.9)	86 (16.2)	253 (26.7)
Haematological malignancy	101 (6.8)	32 (6.0)	69 (7.3)
Organ transplantation	60 (4.1)	37 (7.0)	23 (2.4)
Chronic kidney disease	337 (22.8)	67 (12.6)	270 (28.5)
At risk condition†	411 (27.8)	124 (23.3)	287 (30.3)
COPD	102 (6.9)	29 (5.5)	73 (7.7)
Asthma	71 (4.8)	38 (7.1)	33 (3.5)
Congestive heart failure	94 (6.4)	14 (2.6)	80 (8.4)
Coronary artery disease	109 (7.4)	8 (1.5)	101 (10.7)
Diabetes mellitus	180 (12.2)	49 (9.2)	131 (13.8)
Liver disease	50 (3.4)	28 (5.3)	22 (2.3)
Low-risk†	169 (11.4)	109 (20.5)	60 (6.3)
BMI (median, IQR)	26.6 (23.9–30.6)	27.1 (24.2–31.8)	26.4 (23.8–30)
Smoking			
Current	165 (11.2)	110 (20.7)	55 (5.8)
Former	587 (39.7)	202 (38.0)	385 (40.7)
Missing	20 (1.4)	3 (0.6)	17 (1.8)
Influenza vaccination			
Yes‡	556 (37.6)	109 (20.5)	447 (47.2)
Missing	45 (3.0)	10 (1.9)	35 (3.7)
Pneumococcal vaccination			
PPV23 vaccinated§	324 (21.9)	58 (10.9)	266 (28.1)
PCV13 vaccinated§	68 (4.6)	11 (2.1)	57 (6.0)
Missing	18 (1.2)	4 (0.8)	14 (1.5)
COVID-19 vaccination			
Yes¶	843 (57.0)	224 (42.1)	619 (65.4)

*The denominator used for percentage calculation.
†As defined by the Advisory Committee on Immunization Practices.[16] Patients with chronic medical conditions exclude those concomitant immunocompromising conditions.
‡Vaccinated in past 12 months.
§Vaccinated in past 5 years.
¶At least one dose of COVID-19 vaccine.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.

Table 2 Pathogens detected by per-protocol testing in patients with radiologically confirmed community-acquired pneumonia July 2021 to June 2023

	≥18 years n/N (%)	18–64 years n/N (%)	≥65 years n/N (%)
Bacterial pathogens*			
Streptococcus pneumoniae†	96/1056 (9.1)	34/369 (9.2)	62/687 (9.0)
Legionella spp.‡	7/1479 (0.5)	4/532 (0.3)	3/947 (0.2)
Viral pathogens‡			
SARS-CoV-2	390/1068 (36.5)	170/366 (46.4)	220/702 (31.3)
Rhinovirus	57/1054 (5.4)	25/363 (6.9)	32/691 (4.6)
Parainfluenza virus	35/1054 (3.3)	11/363 (3.0)	24/691 (3.5)
Respiratory syncytial virus	39/1054 (3.7)	9/362 (2.5)	30/692 (4.3)
Human metapneumovirus	25/1054 (2.4)	13/363 (3.6)	12/691 (1.7)
Influenza A or B	19/1054 (1.8)	5/363 (1.4)	14/691 (2.0)
Human endemic coronavirus	16/1054 (1.5)	10/363 (2.8)	6/691 (0.9)
Enterovirus	17/1054 (1.6)	6/363 (1.7)	11/691 (1.6)
Adenovirus	13/1054 (1.2)	5/363 (1.4)	8/691 (1.6)
Bocavirus	4/1054 (0.4)	2/363 (0.6)	2/691 (0.3)

**Haemophilus influenzae* and *S. pneumoniae* were detected by PCR from nasopharyngeal swabs in 68 (4.6%) and 76 (5.1%) of tested patients. Because of the unclear clinical significance of carriage by these bacteria, they are not included in the table.
†Detected by culture, PUAT or UAD1 or UAD2.
‡Detected by multiplex PCR from nasopharyngeal swabs. The result is based on data collection from January 2021 through June 2023; *Legionella* spp.
PUAT, pneumococcal urinary antigen test; UAD, Pfizer serotype-specific urinary antigen detection test.

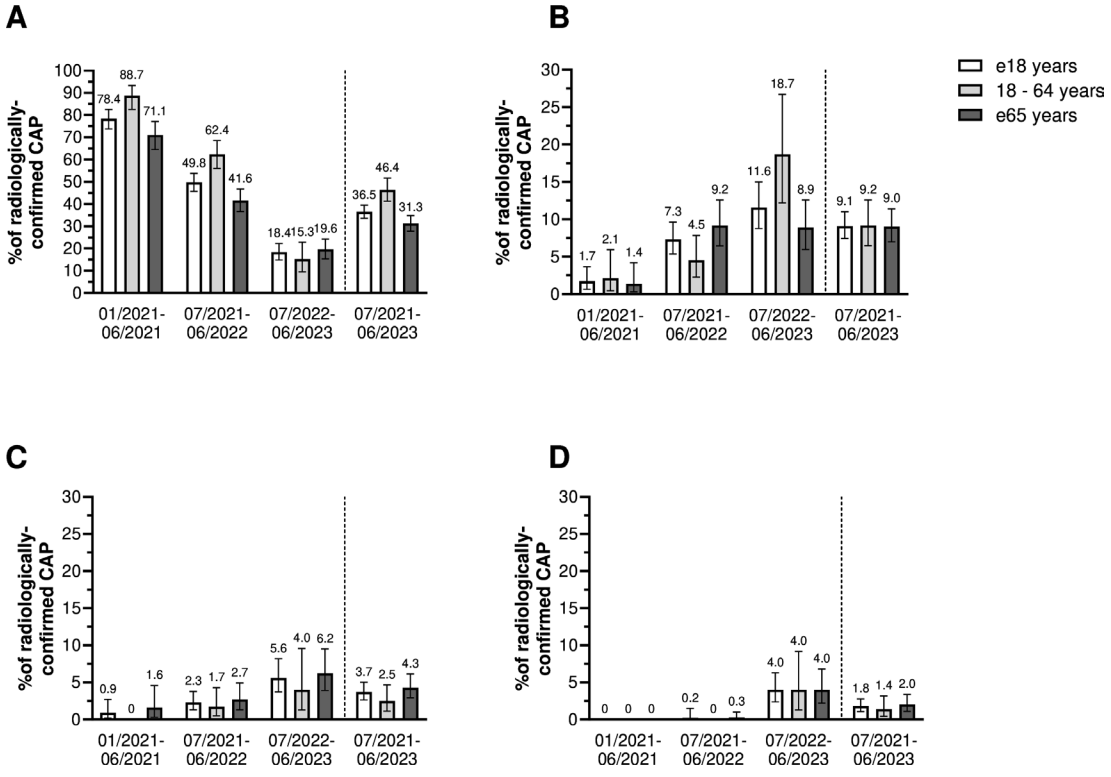

Figure 1 Proportion of radiologically confirmed CAP among study participants due to SARS-CoV-2, *S. pneumoniae*, RSV and influenza A/B by age group and surveillance year in Germany, 2021–2023. (A) SARS-CoV-2, (B) *S. pneumoniae*, (C) RSV and (D) Influenza A/B. CAP, community-acquired pneumonia; RSV, respiratory syncytial virus; *S. pneumoniae*, *Streptococcus pneumoniae*.

Table 3 Pneumococcal serotypes in patients with radiologically confirmed community-acquired pneumonia hospitalised July 2021 to June 2023

	≥18 years n/N (%)	18–64 years n/N (%)	≥65 years n/N (%)
Participants tested for *S. pneumonia* serotype			
Yes	1056*/1116 (94.6)	369*/382 (96.6)	687*/734 (93.6)
Missing	60/1116 (5.4)	13/382 (3.4)	47/734 (6.4)
S. pneumoniae detected by any method†	96/1056 (9.1)	34/369 (9.2)	62/687 (9.0)
S. pneumoniae w/ serotype information‡	79/1056 (7.5)	31/369 (8.4)	48/687 (6.9)
PCV13 serotypes§	49/1056 (4.6)	19/369 (5.1)	30/687 (4.4)
1	8/1056 (0.8)	1/369 (0.3)	7/687 (1.0)
3	24/1056 (2.3)	13/369 (3.5)	11/687 (1.6)
19A	4/1056 (0.4)	0/369 (0.0)	4/687 (0.6)
5	1/1056 (0.1)	1/369 (0.3)	0/687 (0.0)
4	1/1056 (0.1)	1/369 (0.3)	0/687 (0.0)
6A/6C	6/1056 (0.6)	2/369 (0.5)	4/687 (0.6)
6B	1/1056 (0.1)	0/369 (0.0)	1/687 (0.1)
14	4/1056 (0.4)	3/369 (0.8)	1/687 (0.1)
18C	0/1056 (0.0)	0/369 (0.0)	0/687 (0.0)
7F	1/1056 (0.1)	0/369 (0.0)	1/687 (0.1)
9V	0/1056 (0.0)	0/369 (0.0)	0/687 (0.0)
19F	1/1056 (0.1)	0/369 (0.0)	1/687 (0.1)
23F	2/1056 (0.2)	0/369 (0.0)	2/687 (0.3)
PCV15 serotypes§	52/1056 (4.9)	21/369 (5.7)	31/687 (4.5)
PCV15 non-PCV13 serotypes	5/1056 (0.5)	3/369 (0.8)	2/687 (0.3)
22F	5/1056 (0.5)	3/369 (0.8)	2/687 (0.3)
33F	0/1056 (0.0)	0/369 (0.0)	0/687 (0.0)
PCV20 serotypes§	7/10563 (6.9)	30/369 (8.1)	43/687 (6.3)
PCV20 non-PCV15 serotypes§	22/1056 (2.1)	10/369 (2.7)	12/687 (1.7)
8	8/1056 (0.8)	3/369 (0.8)	5/687 (0.7)
11A	5/1056 (0.5)	2/369 (0.5)	3/687 (0.4)
15B/15C	4/1056 (0.4)	3/369 (0.8)	1/687 (0.1)
10A	4/1056 (0.4)	2/369 (0.5)	2/687 (0.3)
12F	1/1056 (0.1)	0/369 (0.0)	1/687 (0.1)
Non-PCV20 serotypes (UAD)	3/1056 (0.3)	1/369 (0.3)	2/687 (0.3)
2	2/1056 (0.2)	0/369 (0.0)	2/687 (0.3)
20	2/1056 (0.2)	1/369 (0.3)	1/687 (0.1)
9N	1/1056 (0.1)	1/369 (0.3)	0/687 (0.0)
17F	1/1056 (0.1)	0/369 (0.0)	1/687 (0.1)
Non-PCV20 serotypes¶ (culture only)	4/1056 (0.4)	1/369 (0.3)	3/687 (0.4)
Unknown serotype**	16/1056 (1.5)	2/369 (0.5)	14/687 (2.0)

Four participants were positive for two serotypes. They contribute to counts for multiple serotypes, but only one time to serotypes grouped by PCV formulation. Hence, counts for individual vaccine serotypes may be higher than for grouped vaccine serotypes.
*Number of participants included in the population, with non-missing UAD results or serotype identified by culture. The values in this row are used as the denominators for percentage of participants.
†Detection methods include: UAD1/UAD2 (serotypes 4, 6A, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6B, 19A, 22F, 33F, 8, 10A, 11A, 12F, 15B, 2, 9N, 17F, 20 plus cross-reactive serotypes 6C and 15C), PUAT, blood culture or respiratory specimen culture.
‡Detection methods include: UAD1/UAD2, blood culture or respiratory specimen culture.
§As serotypes 6A and 6C are identified together as 6A/6C in the UAD1 assay and serotypes 15B and 15C are identified together as 15B/15C in the UAD2 assay, the vaccine-related serotypes 6C and 15C are included serotype counts grouped by vaccine formulation as appropriate.
¶Detected by blood culture or respiratory specimen culture only, serotypes not included in UAD1/UAD2 assay.
**Pneumococci detected by PUAT only.
PCV-13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PUAT, pneumococcal urinary antigen test (BinaxNOW *S. pneumoniae*); UAD, Pfizer serotype-specific urinary antigen detection test.

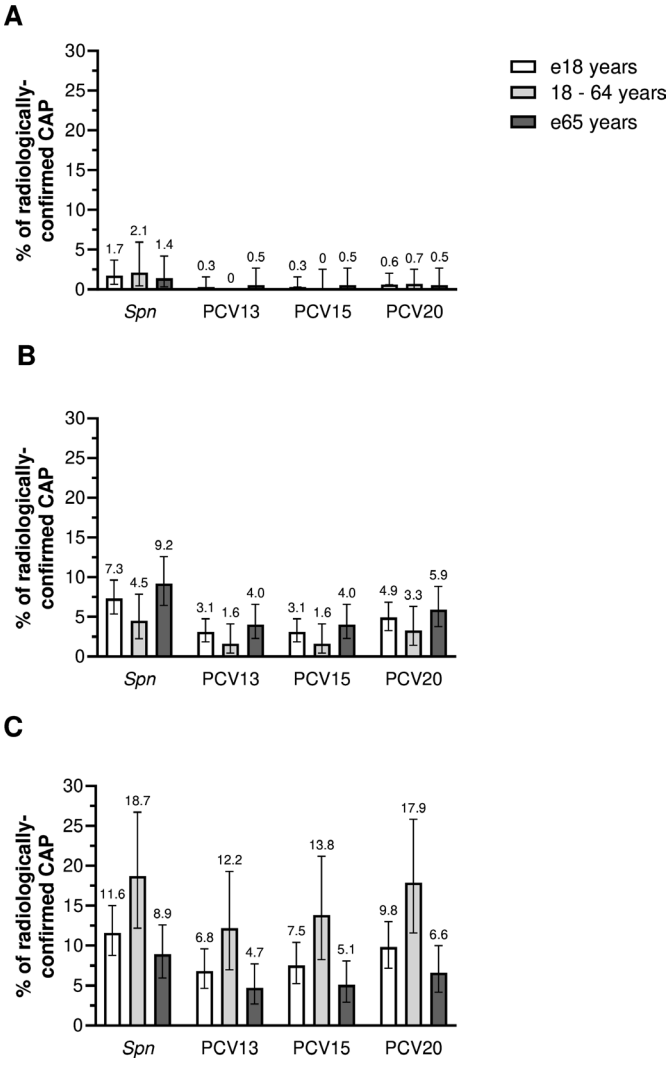

Figure 2 Proportion of radiologically confirmed CAP due to *S. pneumoniae* and serotypes included into PCV13, PCV15 and PCV20 by age group and surveillance year in Germany. (A) January 2021 to June 2021, (B) July 2021 to June 2022 and (C) July 2022 to June 2023. CAP, community-acquired pneumonia. PCV13, 13-valent pneumococcal conjugate vaccine; PCV15, 15-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; *Spn, S. pneumoniae*.

was 490/100 000 (95% CI 461 to 521) in adults aged ≥18 years, ranging from 117/100 000 (95% CI 101 to 1136) to 1538/100 000 (95% CI 1438 to 1643) in patients aged 18–64 years and ≥65 years (figure 3). RAD-CAP annual incidence among adults aged ≥65 years increased from 1113/100 000 (95% CI 1049 to 1180) in 2021 to 1692/100 000 (95% CI 1613 to 1774) in 2022/2023 but decreased from 169/100 000 (95% CI 145 to 197) to 116/100 000 (95% CI 96 to 139) in adults aged 18–64 years (figure 3). Annual incidences of RAD-CAP due to SARS-CoV-2, *S. pneumoniae*, RSV and influenza virus in adults aged ≥18 years between July 2021 and June 2023 were 179/100 000 (95% CI 153 to 205), 44/100 000 (95% CI 31 to 57), 18/100 000 (95% CI 10 to 26) and 8/100 000 (95% CI 3 to 14), respectively. While SARS-CoV-2 incidence decreased, the incidences for *S. pneumoniae*, RSV and influenza virus increased. During the last surveillance year, RAD-CAP incidences in adults aged ≥18 years were 97/100 000 (95% CI 78 to 116) for SARS-CoV-2, 60/100 000 (95% CI 45 to 75) for pneumococcus, 30/100 000 (95% CI 19 to 41) for RSV and 19/100 000 (95% CI 11 to 28) for influenza virus (figure 3). Incidences among adults aged ≥65 years were 8.5-fold higher than in the age group 18–64 years for SARS-CoV-2, 12.4-fold higher for *S. pneumoniae*, 22.0-fold higher for RSV and 13.0-fold higher for influenza. IRs of all-cause RAD-CAP and pathogen-defined RAD-CAP using age group definitions of the RKI are summarised in online supplemental table 10.

DISCUSSION

To our knowledge, this is the first prospective, multicentre, population-based surveillance study on the epidemiology of CAP in Germany at the time of a receding of the COVID-19 pandemic and the resurgence of other pneumonia pathogens. The incidence of RAD-CAP hospitalisations in our study population was high and exceeded local estimates from the pre-pandemic period. An expected drop in COVID-19 incidence between 2021 and 2023 was paralleled with a dramatic increase of CAP due to pneumococcus and RSV, resulting in a net increase of all-cause RAD-CAP by 27% for ≥18 years and 52% for ≥65 years in 2022/2023. The highest burden of RAD-CAP was observed in adults aged ≥65 years, whose incidence of all-cause RAD-CAP was 11.4-fold higher than in 18–64 years old. These findings support the importance of new respiratory vaccines in reducing the morbidity and mortality burden due to CAP in Germany.

The IRs observed among older adults were consistent with meta-estimates of a recent systematic literature review[22] but higher than those derived from German administrative data based on primary ICD-10 discharge codes (1061/100 000).[10] Compared with population-based surveillance studies from Bristol (UK) and Louisville/Kentucky (USA), which reported annual incidences higher than 2000/100 000 adults ≥65 years of age,[23 24] our incidence was lower, which may reflect differences in study period, age-group definitions and healthcare systems. Strikingly, pneumococcal CAP incidence in our study was almost 40-fold higher than official estimates reported by Germany's RKI,[17] consistent with evidence that ICD-10 coding algorithms substantially underdetect pneumococcal pneumonia.[12] These results strongly support the use of studies with prospective microbiological testing using sensitive diagnostic tests for estimating pneumococcal CAP burden.

Post-pandemic resurgence of *S. pneumoniae*,[25 26] RSV[27 28] and influenza virus[4] has been documented in surveillance systems in Europe and globally. Our study quantifies for the first time how recirculation of these pathogens has impacted the overall and vaccine-preventable burden of RAD-CAP. The reduced circulation of various pathogens during the pandemic, particularly RSV, led to a buildup

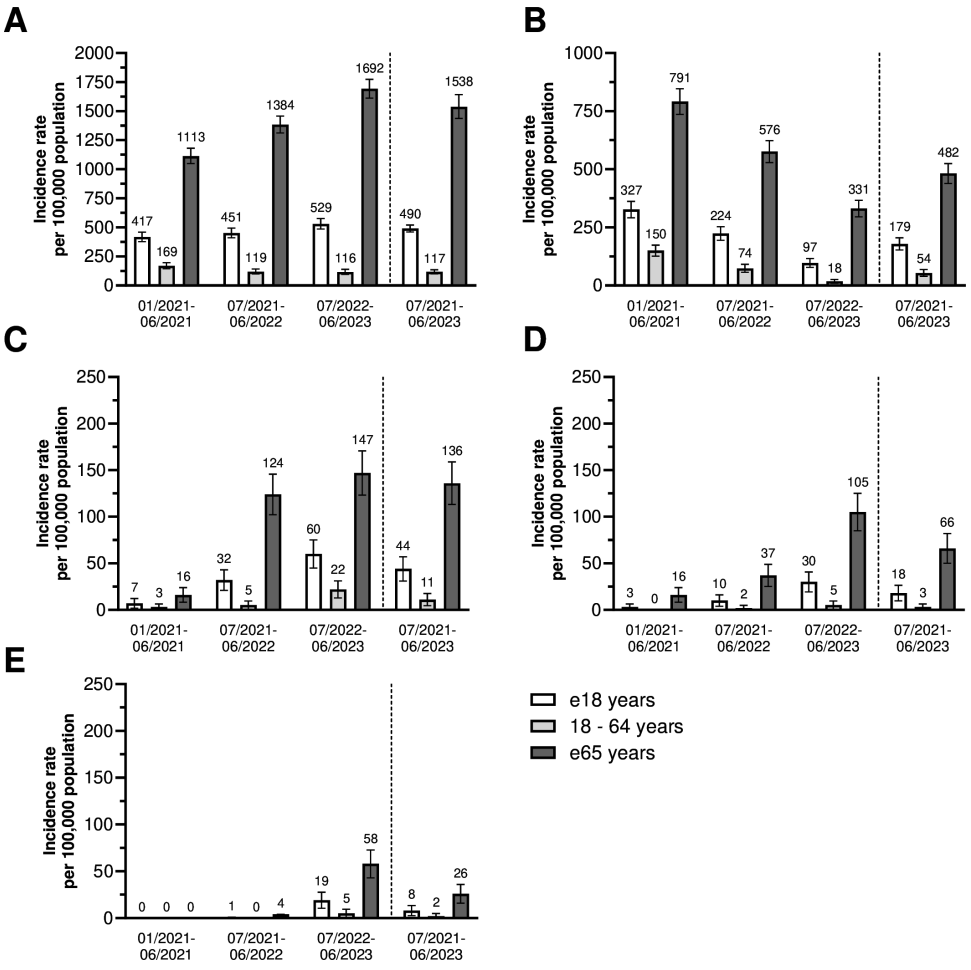

Figure 3 Incidence rate of all-cause and pathogen-specific radiologically confirmed CAP by age group and surveillance year in Germany. (A) All-cause CAP, (B) SARS-CoV-2-related CAP, (C) pneumococcal CAP, (D) RSV-related CAP and (E) influenza A/B-related CAP. CAP, community-acquired pneumonia; RSV, respiratory syncytial virus.

of individuals susceptible to these pathogens in the population.[29] At the same time, relaxation of pandemic restrictions led to reduced mask use, resumption of social gatherings and reopening of workplaces, resulting in more transmission events.[29] Although some caution is advised when interpreting short-term trends from a single study, the 50% increase of RAD-CAP among older adults observed at our surveillance sites suggests that co-circulation of SARS-CoV-2 and other established pneumonia pathogens may have driven overall pneumonia morbidity and mortality above pre-pandemic levels.

Serotypes included in PCV20 detected in RAD-CAP increased from 0.6% in the first 6 months of 2021 to 9.8% in 2022/2023, approaching pre-pandemic levels reported from the German Community-acquired pneumonia Netz (CAPNETZ) study (13.2% in adults in 2018–2019).[30] The proportion of CAP due to PCV20 serotypes in our study population was higher compared with patients hospitalised with CAP in the USA[31] but much lower when compared with the UK.[32] However, both assays use different methods of setting positivity cut-off points.[13 14 33] Resultantly, differences in assay sensitivity and specificity in the two UAD tests likely contribute towards large differences in serotype prevalence in adult CAP.[33]

Our study provides the first prospective estimate of RSV-related CAP hospitalisation incidence among adults in Europe. RSV detection rates of 2.5% and of 4.3% for those aged 18–64 years and ≥65 years in our study, respectively, are aligned with pre-pandemic estimates from the USA and Canada. Given that RAD-CAP only accounts for about one-third of RSV-associated respiratory disease[34 35] hospitalisations, and NP swabs detect approximately half of all RSV cases compared with a multi-specimen testing approach,[35] our incidence estimates likely underestimate the true burden. Underdetection-adjusted incidence of hospitalised RSV-related respiratory tract infections from our previous study was 31/100 000 and 396/100 000 in persons 18–64 and ≥65 years, respectively,[36] and was comparable to Germany-specific estimates from time-series analyses.[37]

Similarly, PCV20-type CAP incidence is likely also underestimated in our study due to limited sensitivity of the UAD assay for non-bacteremic CAP.[38] For example, comparison of PCV13 vaccine-preventable disease incidence for all-cause CAP and UAD-positive CAP incidence in studies conducted between 2008 and 2017 suggests at least a twofold underestimation of PCV13-type CAP by the UAD assay.[30 39–42]

This study had several strengths. Active surveillance using broad screening criteria including physician assessment, radiology and microbiology resulted in nearly complete capture of RAD-CAP cases for incidence estimates of all-cause CAP. A well-defined catchment population, collection of minimal data on non-enrolled study eligible patients and high microbiological testing rates among enrolled patients allowed for more accurate estimations of all-cause and pathogen-defined RAD-CAP incidence. Our study also had limitations. Due to the COVID-19 pandemic, incidence estimates could only be provided for one of three study sites, limiting the generalisability of our results. Difficulties in obtaining informed consent from older and multimorbid patients resulted in a relatively low enrolment rate and selection of somewhat healthier patients into the study. Applying microbiology testing results to the intended study sample assumes similar test-positivity rates for tested and untested patients. Also, PCR testing of NP swabs for RSV[35] and UAD testing for *S. pneumoniae*[38] has limited sensitivity for detection of these pathogens in patients with CAP, leading to likely substantial underestimation of the disease burden. Finally, incomplete ascertainment of vaccination status prevented estimation of IRs stratified by vaccination exposure, limiting the ability to estimate the burden of disease among unvaccinated individuals.

Taken together, the high burden of vaccine-preventable CAP described by our study and persistently low uptake of adult respiratory vaccines (where only 20% and 38% of older adults, respectively, have ever received a pneumococcal or annual influenza vaccine, and 16% are revaccinated for COVID-19 according to recommendations) highlights the need to strengthen respiratory vaccine programmes in Germany.[43] Policy efforts should prioritise older adults and individuals with comorbidities who have the highest risk of disease. Given that when applying the pathogen-specific IRs from our study to the German population, up to 126 000 annual cases of hospitalised CAP are potentially vaccine preventable, increasing vaccine uptake could substantially reduce hospitalisation rates and associated mortality.[44]

In conclusion, the high burden of vaccine-preventable CAP described by our study and the low vaccine uptake among older adults highlight the urgent need to improve the coverage of respiratory vaccines in Germany.

Acknowledgements We would like to thank the JUH study nurses (Stephanie Beier, Jana Schmidt, Janine Wittig and Claudia Merbold), study coordinators (Juliane Ankert, Steffi Kolanos and Susana Cubillos) and study investigators (Christina Bahrs, Sebastian Weis and Anne Möser) for their contributions to the implementation of the study and Rohini Beavon for her support in drafting the study protocol.

Contributors All authors meet the ICMJE criteria for authorship. The specific contributions of each author are as follows: CT, BDG, MWP and SH—conceived and designed the study; contributed to the development of the research question and study protocol. SH, JA, MWP and CS—collected and curated the data. LW, KP and CT—performed data analysis and interpretation. CT—drafted the initial manuscript and contributed to revisions. CT, SH, JP, CS, ACT, CvE, RDW, JV, LW, KP, BDG and MWP—provided critical review of the manuscript for important intellectual content. CS and CT—oversaw project administration and ensured accuracy and integrity of the work. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work. Guarantor: CT.

Funding The study was funded and sponsored by Pfizer. The sponsor was responsible for designing the study, the analysis of study results, the interpretation of the data, the writing of the report; and in the decision to submit the paper for publication. The sponsor was not involved in the collection of the 17 data. The sponsor did not influence the results/outcomes of the study despite author affiliations with the sponsor.

Competing interests CT, CS, CvE, RDW, JV, LW and KP are full-time employees of Pfizer Vaccines and may hold stock and/or stock options. BDG was a Pfizer employee during the conduct and analysis of the study and may hold stock and/or stock options. All other authors have no competing interest to declare.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the JUH Ethics Committee (reference number 2020–1947) and the Ethikkommission Landesärztekammer Thüringen (reference number 47647/2020/157). All study participants or their legal representatives provided written or verbally informed consent. Written informed consent was sought wherever possible. If a potential participant was unable to write, consent could have been given verbally in the presence of an impartial witness. If a participant was unable to read, an impartial witness was present during the entire informed consent discussion.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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