Aus dem Robert Koch-Institut und

der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Evaluation of using ICD-10 code data for RSV surveillance and identification of risk factors for RSV disease

Evaluation von Verwendung der ICD-10 Code Daten für RSV Surveillance und Identifikation von Risikofaktoren für RSV-Erkrankung

zur Erlangung des akademischen Grades

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Abstract (English)

Introduction

Respiratory syncytial virus (RSV) is the common cause of acute lower respiratory tract infection (ALRI) and a major cause of hospital admission for ALRI in young children. The aims of the study were to evaluate the use of RSV specific ICD-10 codes for RSV surveillance and to identify risk factors for hospitalized RSV and its severe outcomes.

Methods

Secondary data analysis was performed based on data of the existing ICD-10-based and virological surveillance systems for acute respiratory infections (ARI) in Germany. The data of ICD-10-based and virological surveillance in primary care were matched. Sensitivity and specificity of RSV specific ICD-10 codes for the identification of laboratory-confirmed RSV infections were calculated. Based on data of the ICD-10-based surveillance in secondary care, univariable and multivariable logistic regression analysis was performed to assess age group, gender, season and underlying medical conditions as possible risk factors for hospitalized RSV and its severe outcomes including ICU admission, application of ventilator support and death.

Results

Data of 1,087,243 ARI consultations and 23,834 respiratory specimens in the surveillance systems in primary care could be analyzed. Of these, 2,624 ARI cases could be matched. The RSV specific ICD-10 codes had poor sensitivity (6%, 95%-CI:3%-12%), and high specificity (99.8%, 95%-CI:99.6%-99.9%). In children <5 years within RSV seasons, the sensitivities of RSV specific ICD-10 codes when combined with general ALRI ICD-10 codes J18.-, J20.- and with J12.-, J18.-, J20.-, J21.-, J22 increased 7-fold (44%, 95%-CI:30-59%). The specificities of both combinations remained high (91%, 95%-CI:86-94%; 90%, 95%-CI:85-94%). Based on the ICD-10 surveillance data in secondary care, 413,552 severe ARI (SARI) cases and 8,761 RSV cases were identified. Among SARI cases aged <5 years, the age group <1 year, underlying respiratory and cardiovascular disorders specific to the perinatal period were risk factors for being diagnosed with RSV. In age group >=5 years, underlying congenital defect originating in perinatal period, cystic fibrosis, vitamin D deficiency and chronic pulmonary disease were risk factors for being

diagnosed with RSV. Age groups 0-5 months and >=65 years, low birth weight, preterm newborn, underlying respiratory and cardiovascular disorders specific to the perinatal period, congenital malformation of the heart and great vessels, congenital defect originating in perinatal period, cystic fibrosis, chronic pulmonary disease, cardiovascular disease, neurological disorders, blood disease, liver disease and renal failure were risk factors for severe outcomes of RSV disease.

Conclusions

RSV specific ICD-10 codes underestimate the number of actual RSV diseases. This can be overcome by combining RSV specific and general ALRI ICD-10 codes. Using ICD-10-based surveillance data allows identifying risk factors for hospitalized RSV and its severe outcomes.

Abstract (German)

Einleitung

Das Respiratorische Syncytial-Virus (RSV) ist der häufigste Erreger von akuten Erkrankungen der unteren Atemwege (AEUA) bei Kleinkindern. Diese Arbeit evaluierte die Verwendung der RSV-spezifischen ICD-10-Codes für RSV-Surveillance und identifizierte Risikofaktoren für hospitalisierte RSV-Erkrankung und ihre schweren Outcomes.

Methodik

Sekundärdatenanalyse wurde basierend auf den Daten von ICD-10-basierten und virologischen Surveillance-Systemen für akute respiratorische Erkrankungen (ARE) der Primär- und Sekundärversorgung in Deutschland durchgeführt. Die Sensitivität und Spezifität von RSV-spezifischen ICD-10-Codes zur Identifizierung von laborbestätigen RSV-Erkrankungen wurden berechnet. Mit den ICD-10-basierten Surveillance-Daten wurde univariable und multivariable logistische Regressionsanalyse durchgeführt, um Risikofaktoren für hospitalisierte RSV-Erkrankung und ihre schweren Outcomes (Intensivbehandlung, Beatmung und Tod) auszuwerten.

Ergebnisse

Daten von 1.087.243 ARE-Konsultationen und 23.834 Atemproben in den Surveillance-Systemen in der Primärversorgung konnten analysiert werden. Davon konnten 2.624 ARE-Fälle abgeglichen werden. Die RSV-spezifischen ICD-10-Codes hatten eine niedrige Sensitivität (6%, 95%-KI:3%-12%) und hohe Spezifität (99,8%, 95%-KI:99,6%-99,9%). Die Sensitivitäten erhöhten sich in Kombination mit den allgemeinen AEUA ICD-10-Codes J18.-, J20.- und J12.-, J18.-, J20.-, J21.-, J22 (44%, 95%-KI:30-59%) bei Kindern <5 Jahren während der RSV-Saison. Die Spezifitäten beider Kombinationen blieben hoch (91%, 95%-KI:86-94%; 90%, 95%-KI:85-94%). Basierend auf den ICD-10-Code-Daten in der Sekundärversorgung wurden 413.552 schwere ARE (SARI)-Fälle und 8.761 RSV-Fälle identifiziert. Bei SARI-Fällen <5 Jahren alt, die Altersgruppe <1 Jahr, Krankheiten des Atmungs- und Herz-Kreislaufsystems, die für die Perinatalperiode spezifisch sind waren Risikofaktoren für RSV-Erkrankung. Bei Altersgruppe >=5 Jahre, angeborene Fehlbildungen, die für die Perinatalperiode spezifisch sind, Mukoviszidose,

Vitamin-D-Mangel und chronische Lungenerkrankung waren Risikofaktoren für RSV-Erkrankung. Altersgruppen 0-5 Monate und >=65 Jahre, niedriges Geburtsgewicht, Frühgeburt, Krankheiten des Atmungs- und Herz-Kreislaufsystems, die für die Perinatalperiode spezifisch sind, angeborene Fehlbildung des Herzens und der großen Gefäße, angeborener Defekt mit Ursprung in der Perinatalperiode, Mukoviszidose, chronische Lungenerkrankung, Herz-Kreislauf-Erkrankung, neurologische Erkrankung, Bluterkrankung, Lebererkrankung und Nierenversagen waren Risikofaktoren für schwere Outcomes von RSV-Erkrankung.

Schlussfolgerungen

RSV-spezifische ICD-10-Codes unterschätzen die Anzahl der tatsächlichen RSV-Erkrankungen. Dies kann durch die Kombination der RSV-spezifischen und allgemeinen AEUA ICD-10-Codes gelöst werden. Durch ICD-10-basierte Surveillance-Daten können Risikofaktoren für hospitalisierte RSV-Erkrankung und ihre schweren Outcomes identifiziert werden.

1 Introduction

Respiratory syncytial virus (RSV) is a single-stranded, negatively oriented and unsegmented RNA virus of the family Pneumoviridae. RSV can be subtyped into Type A and Type B. Viral strains of both subtypes circulate simultaneously [1]. Based on the virological surveillance data in Germany, RSV B dominated in the seasons 2018/19 (60%) and 2017/18 (66%), RSV A dominated in the season 2016/17 (63%) [2].

RSV is a worldwide distributed pathogen of acute respiratory infection (ARI) of all ages. Adults with RSV may often have asymptomatic infection or mild symptoms of upper respiratory tract infection. In infants, young children and older adults, RSV infection often spreads to the lower respiratory tract. RSV is the most common cause of bronchiolitis and pneumonia within the first year of life [1, 3-5]. By the end of the first year of life, 50-70% and by the end of the second year of life almost all children are infected with RSV at least once. RSV is also a major cause of hospital admission for acute lower respiratory tract infection (ALRI) in infants and young children [3, 5]. Worldwide in 2015, 21.6-50.3 million RSV-associated ALRI episodes occurred in children younger than 5 years, with about 2.7-3.8 million hospital admissions [4]. The transmission takes place normally through droplet infection from an infectious person to a contact person. RSV disease has similar seasonality as influenza. In Central Europe, the RSV season is normally from November to April of the following year. The peak of the RSV season lasts about 4-8 weeks and is mostly in January and February [5]. Some studies indicated that besides some socio-demographic and environmental factors, underlying medical conditions were associated with an increased risk of being infected with RSV [5-8]. Furthermore, underlying medical conditions may predispose young children to severe RSV disease [7, 9, 10].

Currently, only passive immunization with the monoclonal antibody palivizumab is available for children at high risk, no vaccine against RSV is approved [1]. In 2015, the World Health Organization (WHO) Product Development for Vaccines Advisory Committee highlighted the development of RSV vaccines for global use [11]. Clinical trials for RSV vaccines and long-acting monoclonal antibodies for passive immunization are underway. Several novel RSV vaccines are expected to enter the market in the next years [11, 12].

RSV is not notifiable in Germany. The sentinel system of the German Working Group on Influenza (AGI) at the Robert Koch Institute (RKI) with its syndromic ARI surveillance and

virological surveillance of respiratory pathogens is a central instrument of influenza and ARI surveillance in primary care in Germany [2]. This system has been linked with a sentinel electronic data collection system for ARI ($SEED^{ARE}$) based on the 10^{th} revision of International Classification of Diseases (ICD-10) codes [2, 13, 14]. The software module for the electronic recording of ICD-10 codes is based on an interface developed by the RKI, which was implemented in five physician information systems in primary care [14]. ICD-based syndromic surveillance is a relatively novel approach, compared to the traditional surveillance. It has been shown to capture and transmit data rapidly, and provide very early warning of potential public health threats [15]. In secondary care, the RKI established an ICD-10-based surveillance system for severe ARI (ICOSARI) in cooperation with a private hospital network in Germany [16]. Data on medical consultations and hospitalizations with any of the RSV specific ICD-10 code diagnoses (J12.1 RSV pneumonia, J20.5 acute bronchitis due to RSV, J21.0 acute bronchiolitis due to RSV) have been collected through $SEED^{ARE}$ and ICOSARI, respectively [2, 13, 14, 16].

The planning of RSV vaccination strategies and the evaluating RSV vaccination impact in the future rely on timely epidemiological data and long-term observation of epidemiological situation of RSV through large scale RSV surveillance systems. Data of the RSV specific ICD-10 codes derived from the ICD-10-based syndromic surveillance systems at the RKI can be used for these purposes. However, the validity of RSV specific ICD-10 codes for RSV surveillance is unclear. So far, only few studies have looked at accuracy of RSV specific ICD-10 codes for the identification of true RSV infections [17]. Risk groups of severe RSV will benefit most from the RSV immunization once RSV vaccines become available. So far, underlying medical conditions have not been assessed comprehensively as risk factors for hospitalized RSV and its severe outcomes, and inconsistent results have been shown for some underlying medical conditions [8].

The aims of this doctoral thesis were

(1) to evaluate using RSV specific ICD-10 codes for RSV surveillance and
(2) to identify risk factors, in particular underlying medical conditions as risk factors for being diagnosed with RSV based on the ICD-10 data,
    1) to identify risk factors for hospitalized RSV disease
    2) to identify risk factors for severe outcomes of RSV disease

in order to contribute to planning of the RSV vaccination strategies and evaluation of RSV vaccination impact in the future.

2 Methods

2.1 Study data

Secondary data analysis was performed based on the anonymized data derived from ICD-10-based surveillance systems SEED^{ARE} and ICOSARI, and from the virological surveillance at the RKI. An overview of characteristics of these surveillance systems is given in Table 1. The SEED^{ARE} system was approved by the German Federal Commissioner for Data Protection and Freedom of Information, and the ICOSARI system by the RKI and HELIOS Kliniken GmbH data protection authority [14, 16]. The virological surveillance activities were approved by the German Federal Commissioner for Data Protection and Freedom of Information and the Ethical Committee of the Charité, Universitätsmedizin, Berlin.

Table 1 ICD-10-based and virological surveillance systems for influenza and ARI at the RKI, Germany

	Surveillance participants	Region of participants	Data collection
Primary care			
Sentinel electronic data collection system for ARI based on ICD-10 codes (SEED^{ARE})	193 practices (2007-2017) • 107 general practices; • 46 pediatric practices; • 26 internist practices; • 14 practices with different specialties	16 federal states	Digital data of medical consultations with any of ARI ICD-10 code diagnoses (J00-J22, J44.0, B34.9) Collected data: age, gender, region, ICD-10 code diagnosis, consultation date, information on inability to work, hospitalization, influenza vaccination status Once a week
Virological surveillance	222 practices (2010-2017)	16 federal states	• Pediatric practices: 3 respiratory specimens of patients with ARI or influenza like illness (ILI) per practice • General and internist practices: 5 respiratory specimens of patients with ARI or ILI per practice Collected data: age, gender, region, sampling date, symptom, laboratory finding Once a week
Secondary care			
ICD-10 based hospital surveillance for severe acute respiratory infections (ICOSARI)	84 hospitals (2009-2018)	13 federal states	Digital data of hospitalizations with any of respiratory ICD-10 code diagnoses (chapter X: J00-J99) as primary or secondary discharge diagnosis Collected data: age, gender, region, primary and secondary discharge ICD-10 code diagnoses, admission ICD-10 code diagnoses, admission date, discharge date, length of hospital stay, ICU stay and ventilation, discharge mode Weekly updated

2.2 Methods for evaluation of using ICD-10 codes for RSV surveillance

The use of ICD-10 codes for RSV surveillance was evaluated based on the SEED^{ARE} and the virological surveillance data.

Based on SEED^{ARE} data, a RSV case was defined as a medical consultation with any of the RSV specific ICD-10 code diagnoses (J12.1, J20.5 and J21.0) [13]. Based on the virological surveillance data, a confirmed-RSV-case was defined as the detection of RSV RNA in a respiratory specimen in a patient by real-time reverse transcriptase polymerase chain reaction (rtRT-PCR) [18]. RSV season was defined in line with literature as the weeks when the cumulative number of RSV cases exceeded 1.2% of total RSV cases during the observed period of a surveillance system. One gap week below the threshold was allowed [19, 20].

The sentinel practices participating in both SEED^{ARE} and the virological surveillance were selected by practice-ID. The medical consultations of SEED^{ARE} were matched with respiratory specimens of virological surveillance by practice-ID, age, gender, consultation date and sampling date. Only one-to-one matches were included for the further data evaluation. Sensitivity was calculated as the proportion of cases diagnosed with RSV specific ICD-10 codes among laboratory confirmed-RSV-cases, and specificity as the proportion of cases without RSV specific ICD-10 codes among RSV-negative cases. Sensitivities and specificities of RSV specific ICD-10 codes were calculated among young children (<2 years and <5 years of age), during RSV seasons, and combined with different general ARI ICD-10 codes, respectively. The sensitivities and specificities were calculated with 95%-confidence interval (95%-CI). Stata® (version 15) was used for the data analysis.

2.3 Methods for identification of risk factors for RSV and its severe outcomes

Risk factors for hospitalized RSV and its severe outcomes were identified based on the ICOSARI database.

A severe ARI (SARI) case was defined as a patient hospitalized with any of the ARI ICD-10 codes J09-J22 as primary or secondary discharge diagnosis [13, 16]. A RSV case (hospitalized RSV, severe RSV) was defined as a SARI case diagnosed with any of the RSV specific ICD-10 codes (J12.1, J20.5, J21.0) as primary or secondary discharge diagnosis [13]. ICU admission, application of ventilator support and death were considered as severe outcomes of hospitalized RSV disease.

The hospital network of ICOSARI includes 45 original sentinel hospitals and additional 42 hospitals joined the hospital network after 2013. Due to the possible inconsistent recording practices in the sentinel hospitals, data on ICU admission and application of ventilator support were excluded from the data evaluation for the original sentinel hospitals before 2013 and for the additional sentinel hospitals before 2015.

The specific ICD-10 codes of the underlying medical conditions chosen for the data analysis were adapted from the Elixhauser and Fleming Comorbidity Indices (Table 2) [21, 22, 23].

Table 2 ICD-10 codes of underlying medical conditions [23]

Medical condition	ICD-10 code
Disorder of newborn related to slow fetal growth and fetal malnutrition	P05.-
Extremely low birth weight (<1000 grams)	P07.0-
Low birth weight (1000-2499 grams)	P07.1-
Extreme immaturity of newborn (<28 weeks)	P07.2
Preterm newborn (28-37 weeks)	P07.3
Respiratory and cardiovascular disorder specific to the perinatal period	P20-P29
Congenital malformation of the heart	Q20-Q24
Congenital malformation of the great vessels	Q25-Q26
Congenital defect originating in perinatal period	Q02, Q30.-, Q32-Q37, Q44.-, Q60.-, Q61.-, P70.0, P70.1, P70.2, P78.8
Down syndrome	Q90.-
Sickle-cell disorder	D57.-
Cystic fibrosis	E84.-
Vitamin D deficiency	E55.-
Asthma	J45.-, J46
Chronic obstructive pulmonary disease (COPD)	J44.-
Chronic pulmonary disease (excl. asthma and COPD)	I27.8, I27.9, J40-J43, J47, J60-J67, J68.4, J70.1, J70.3
Diabetes	E10-E14
Cardiovascular disease	A52.0, I05-I08, I09.1, I09.8, I09.9, I10, I11, I13, I15, I25.5, I26, I27, I28.0, I28.8, I28.9, I34-I39, I42.0, I42.5, I42.9, I43, I44.1-I44.3, I45.6, I45.9, I47-I50, P29.0, Q23.0-Q23.3, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0, Z95.2, Z95.4
Neurological disorders	G10-G13, G20, G22, G25.4, G25.5, G31.2, G31.8, G31.9, G32, G35-G37, G40, G41, G93.1, G93.4, R47.0, R56
Blood disease	D50.0, D50.8, D50.9, D51-D53, D65-D68, D69.1, D69.3-D69.6
Renal failure	I12.0, I13.1, N18, N19, N25, Z49.0, Z49.2, Z94.0, Z99.2
Liver disease	B18, I85, I86, I98, K70, K71.1, K71.3, K71.5, K71.7, K72, K74, K76.0, K76.2, K76.9, Z94.4
Tuberculosis	A15-A19
Cancer	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C85, C88, C96, C90.0, C90.2, C97
HIV/AIDS	B20-B22, B24
Pregnancy	O00-O99

Univariable and multivariable logistic regression analysis was carried out to assess age group, gender, season and underlying medical conditions as possible risk factors for being diagnosed with RSV among SARI cases, for ICU admission, application of ventilator support, and death among RSV cases, respectively. The analysis was stratified in two age groups <5 and >=5 years. Odds ratios (OR) were calculated and presented with 95%-CI. A p value of <0.05 was considered statistically significant. Only variables indicating significant associations with RSV or any severe outcomes of RSV in univariable logistic regression models were kept in multivariable models, respectively. Stata® (version 15) was used for the data analysis.

3 Results

3.1 Evaluation of using of ICD-10 codes for RSV surveillance

3.1.1 Descriptive analysis of RSV cases based on SEED^{ARE}

From week 40/2007-13/2017, 1,087,243 ARI consultations were collected by the SEED^{ARE} system. Among them, 1,165 (0.11%) received a RSV specific ICD-10 code. Among ARI cases aged <2 years, 765 (0.44%) received a RSV specific ICD-10 code. Among the RSV cases, 66% (765) were children aged <2 years. In this age group, the number of RSV cases was higher in boys (423) than in girls (339; Table 3). The cumulative number of the RSV cases peaked in the 8th week (88) within the observed period. The RSV season on average was from 41-16 week. The number of RSV cases was highest in the season 2016/17 within the observed period.

3.1.2 Descriptive analysis of confirmed-RSV-cases based on virological surveillance

Among 23,834 respiratory specimens tested for RSV in the virological surveillance of the AGI from week 40/2010-18/2017, 1,785 (8%) were RSV positive. The RSV positive rate (25%, 659) was highest among children aged <2 years. In this age group, the number of confirmed-RSV-cases was higher among boys (378) than girls (270; Table 3). Within the observed period, the cumulative number of confirmed-RSV-cases peaked in the 6th week (143). The RSV season on average was from 48-15 week. The number of confirmed-RSV-cases was also highest in the season 2016/17 within the observed period.

Table 3 Comparision of RSV cases based on SEED^{ARE} (week 40/2007-13/2017) und confirmed-RSV-cases based on virological surveillance (week 40/2010-18/2017) by age group and gender

	RSV cases based on SEED^{ARE}			Confirmed-RSV-cases based on virological surveillance			
Age group (yr)	**Male n (%)**	**Female n (%)**	**Total n (%)**	**Male n (%)**	**Female n (%)**	**Total n (%)**	**Positive rate (%)**
0-1	423 (69)	339 (62)	765 (66)	378 (40)	270 (33)	659 (37)	25
2-4	92 (15)	90 (16)	184 (16)	260 (28)	259 (31)	522 (29)	16
5-14	32 (5)	28 (5)	60 (5)	86 (9)	67 (8)	153 (9)	3
15-34	27 (4)	33 (6)	60 (5)	54 (6)	44 (5)	98 (5)	2
35-59	28 (5)	42 (8)	70 (6)	96 (10)	104 (13)	201 (11)	3
>=60	10 (2)	16 (3)	26 (2)	64 (7)	80 (10)	145 (8)	6
Total	612	548	1,165	941	827	1,785	8

3.1.3 Sensitivity and specificity of RSV specific ICD-10 codes for the identification of laboratory-confirmed RSV infections

From week 40/2010-13/2017, 48 sentinel practices participated in both SEED^{ARE} and the virological surveillance systems. In the 48 practices, 7% (400/5,589) of the respiratory specimens were RSV positive, and 2,624 (47%) respiratory specimens could be matched with the medical consultations based on SEED^{ARE} system (Figure 1).

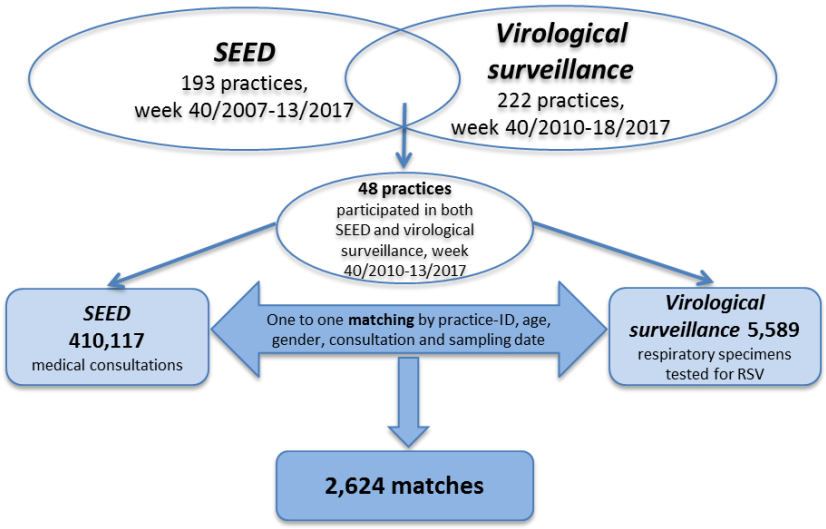

Figure 1 Matching of data from SEED^{ARE} and virological surveillance, week 40/2010-13/2017 [24]

The sensitivity of RSV specific ICD-10 codes was 6% (95%-CI: 3%-12%), and the specificity was 99.8% (95%-CI: 99.6%-99.9%). The sensitivities of RSV specific ICD-10 codes when combined with general ALRI ICD-10 codes J18.-, J20.- and with J12.-, J18.-, J20.-, J21.-, J22 in children aged <5 years within RSV seasons (based on the virological

data 48–15 week) both reached 44% (95%-CI: 30-59%), the specificities of the two combinations were 91% (95%-CI: 86-94%) and 90% (95%-CI: 85-94%), respectively.

Table 4 Sensitivities and specificities of RSV specific ICD-10 codes combined with different general ARI ICD-10 codes, week 40/2010-13/2017 [24]

	Sensitivity		Specificity	
	%	**95%-CI**	**%**	**95%-CI**
RSV codes[1]	6	3-12	99.8	99.6-99.9
<2 years of age				
RSV codes	8	2-22	99.4	95.6-99.9
<5 years of age				
RSV codes	14	6-26	99.6	98-99.9
In RSV seasons[2]				
RSV codes	7	3-12	99.8	99.5-99.9
<5 years of age within RSV seasons				
RSV codes	16	7-29	99.5	98-99.5
RSV codes + J06.-[3]	48	34-63	62	55-68
RSV codes + J11.-[4]	30	18-45	75	68-80
RSV codes + J12.-[5]	16	7-29	99.5	98-99.9
RSV codes + J18.-[6]	30	18-45	98	95-99
RSV codes + J20.-[7]	30	18-45	92	88-95
RSV codes + J21.-[8]	16	7-29	99.5	98-99.9
RSV codes + J22	16	7-29	99	97-99.9
RSV codes + B34.9	28	16-42	80	74-85
RSV codes + J18.-, J20.-	44	30-59	91	86-94
RSV codes + J18.-, J20.-, B34.9	56	41-70	72	65-77
RSV codes + J11.-, J18.-, J20.-, B34.9	62	47-75	48	42-55
RSV codes + J12.-, J18.-, J20.-, J21.-, J22	44	30-59	90	85-94
RSV codes + all general ARI codes[9]	90	78-97	16	11-21

[1]RSV codes: RSV specific ICD-10 codes J12.1, J20.5, J21.0
[2]RSV season: 48-15 week
[3]J06.-: J06, J06.0, J06.8, J06.9
[4]J11.-: J11, J11.0, J11.1, J11.8
[5]J12.-: J12, J12.8, J12.9
[6]J18.-: J18, J18.0, J18.8, J18.9
[7]J20.-: J20, J20.8, J20.9
[8]J21.-: J21, J21.8, J21.9
[9]all general ARI codes: J06, J06.0, J06.8, J06.9, J11, J11.0, J11.1, J11.8, J12, J12.8, J12.9, J18, J18.0, J18.8, J18.9, J20, J20.8, J20.9, J21, J21.8, J21.9, J22, B34.9

3.2 Identification of risk factors for hospitalized RSV and its severe outcomes

3.2.1 Descriptive analysis of RSV cases based on ICOSARI

3.2.1.1 RSV cases among SARI cases

From week 01/2009-20/2018, 1,685,235 respiratory disease hospitalizations were collected by ICOSARI. Among them, 413,552 SARI cases were identified, 56% (232,340) of them were male, and 64% (263,133) were >=65 years old. Of the SARI cases, 8,761 (2%) were RSV cases. Of the RSV cases, 57% were male, and 97% (4,955) were <5 years old (8,521). Of the total RSV cases, 6,773 were from the original sentinel hospitals after 2013 or from the additional sentinel hospitals after 2015 and with information on ICU admission and application of ventilator support (Figure 2, Table 5).

3.2.1.2 ICU admitted RSV cases, ventilated RSV cases and deceased RSV cases

Of the 6,773 RSV cases, 7% (492) were admitted to ICU during the study period. During the ICU stay, 38% (185) required ventilator support, and 3% (15) died in hospital (Figure 2). Of the total admitted RSV cases, 0.3% (25) died in hospital (Table 5).

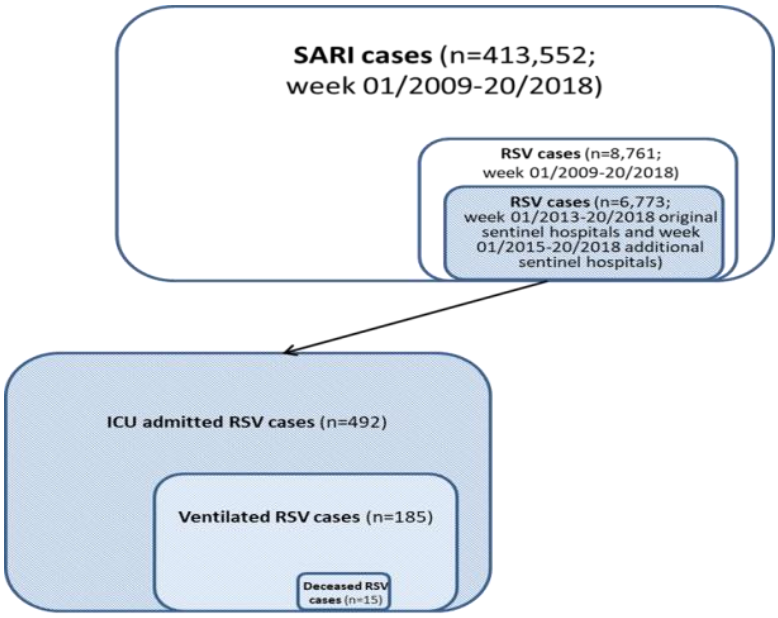

Figure 2 Number of SARI cases, RSV cases, ICU admitted RSV cases, ventilated RSV cases and deceased RSV cases [23]

Table 5 RSV cases and RSV cases with severe outcomes by age group and gender (RSV cases and deceased RSV cases: week 01/2009-20/2018; ICU admitted RSV cases and ventilated RSV cases: week 01/2013-20/2018 original sentinel hospitals, week 01/2015-20/2018 additional sentinel hospitals) [23]

	RSV cases		ICU admitted RSV cases		Ventilated RSV cases		Deceased RSV cases	
	Male	Female	Male	Female	Male	Female	Male	Female
Age group	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
0-5 months	2684 (54)	2099 (55)	164(63)	164 (71)	61 (60)	53 (63)	0 (0)	3 (19)
6 months-1 year	1875 (38)	1338 (35)	54 (21)	35 (15)	17 (17)	10 (12)	2 (22)	3 (19)
2-4 years	273 (6)	252 (7)	12 (5)	9 (4)	3 (3)	5 (6)	1 (11)	1 (6)
5-64 years	62 (1)	56 (1)	13 (5)	5 (2)	6 (6)	2 (2)	1 (11)	2 (13)
>=65 years	61 (1)	61 (2)	19 (7)	17 (7)	14 (14)	14 (17)	5 (56)	7 (44)
Total	4955	3806	262	230	101	84	9	16

3.2.1.3 RSV cases by calendar week

Within the observed period, 2016/17 was the season with the highest number of cases (Figure 3).

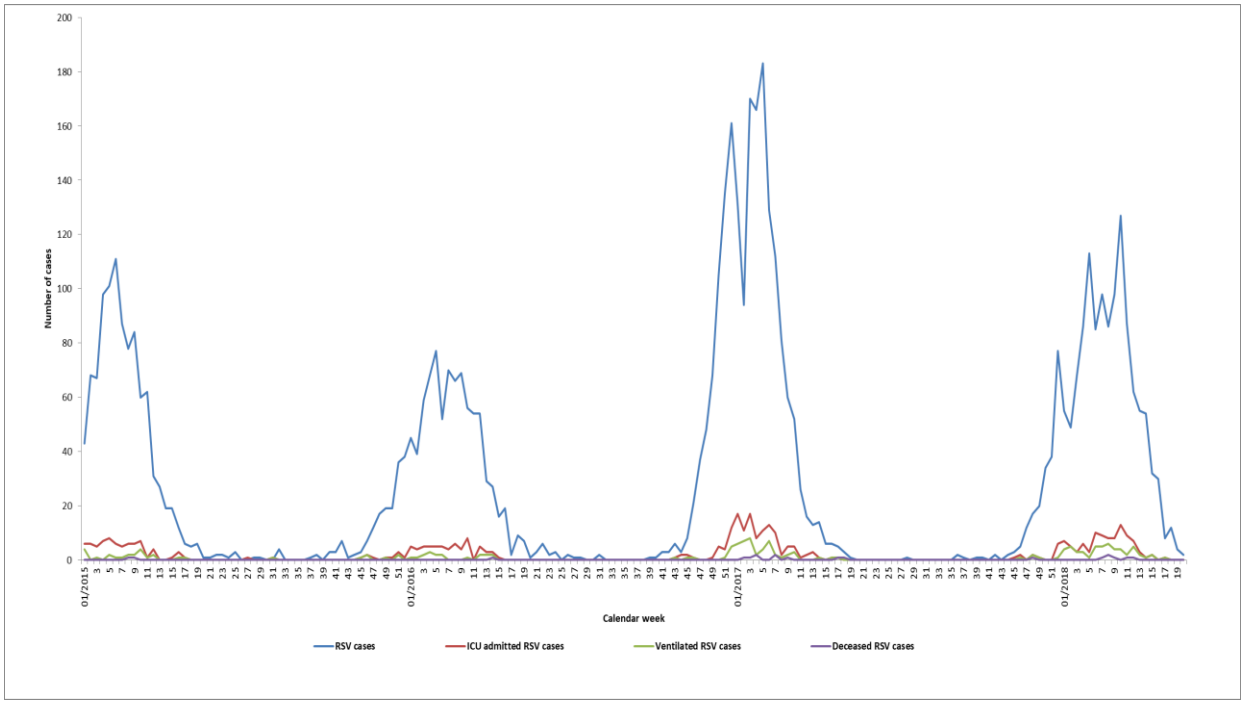

Figure 3 Number of RSV cases and RSV cases with severe outcomes by calendar week, week 01/2015-20/2018 [23]

3.2.1.4 RSV cases with underlying medical conditions

The proportion of total RSV cases with underlying respiratory and cardiovascular disorders specific to the perinatal period (3.5%, 282) was higher than with other underlying medical conditions. The proportion of different underlying medical conditions varied from 0-3.5% (Table 6).

Table 6 RSV cases and RSV cases with severe outcomes by underlying medical condition (RSV cases and deceased RSV cases: week 01/2009-20/2018; ICU admitted RSV cases and ventilated RSV cases: week 01/2013-20/2018 original sentinel hospitals, week 01/2015-20/2018 additional sentinel hospitals) [23]

	RSV cases (n=8761) n (%)	ICU admitted RSV cases (n=492) n (%)	Ventilated RSV cases (n=185) n (%)	Deceased RSV cases (n=25) n (%)
Disorder of newborn related to slow fetal growth and fetal malnutrition	6 (0.1)	1 (0.2)	0	0
Extremely low birth weight (<1000 grams)	9 (0.1)	3 (0.6)	3 (1.6)	0
Low birth weight (1000-2499 grams)	51 (0.6)	16 (3.4)	12 (6.5)	0
Extreme immaturity of newborn (<28 weeks)	8 (0.1)	3 (0.6)	3 (1.6)	0
Preterm newborn (28-37 weeks)	62 (0.8)	21 (4.4)	14 (7.6)	0
Respiratory and cardiovascular disorder specific to the perinatal period	282 (3.5)	60 (12.7)	35 (19.0)	1 (4.0)
Congenital malformation of the heart	131 (1.6)	35 (7.4)	19 (10.3)	2 (8.0)
Congenital malformation of the great vessels	34 (0.4)	13 (2.8)	8 (4.4)	0
Congenital defect originating in perinatal period	61 (0.7)	14 (2.9)	8 (4.3)	1 (4.0)
Down syndrome	42 (0.5)	9 (1.9)	2 (1.1)	0
Sickle-cell disorder	2 (0.0)	0	0	0
Cystic fibrosis	9 (0.1)	1 (0.2)	1 (0.5)	0
Vitamin D deficiency	13 (0.2)	3 (0.6)	3 (1.6)	1 (4.0)
Asthma	63 (0.7)	4 (0.8)	1 (0.5)	0
Chronic obstructive pulmonary disease (COPD)	43 (0.5)	11 (2.2)	8 (4.3)	3 (12.0)

Chronic pulmonary disease (excl. asthma and COPD)	54 (0.6)	5 (1.0)	5 (2.7)	2 (8.0)
Diabetes	62 (0.7)	16 (3.3)	12 (6.5)	4 (16.0)
Cardiovascular disease	222 (2.5)	69 (14.0)	47 (25.4)	15 (60.0)
Neurological disorders	167 (1.9)	34 (6.9)	18 (9.7)	8 (32.0)
Blood disease	129 (1.5)	33 (6.7)	25 (13.5)	9 (36.0)
Renal failure	65 (0.7)	22 (4.5)	14 (7.6)	6 (24.0)
Liver disease	24 (0.3)	8 (1.6)	5 (2.7)	5 (20.0)
Tuberculosis	2 (0.0)	1 (0.2)	1 (0.5)	0
Cancer	27 (0.3)	4 (0.8)	2 (1.1)	1 (4.0)
HIV/AIDS	0	0	0	0
Pregnancy	1 (0.0)	0	0	0

3.2.2 Identification of risk factors for RSV and its severe outcomes

3.2.2.1 Risk factors for RSV and its severe outcomes in age group <5 years

In multivariable analysis, among SARI cases aged <5 years, the age group 0-1 year, being female, underlying respiratory and cardiovascular disorder specific to the perinatal period were significantly associated with an increased risk of being diagnosed with RSV. Among RSV cases aged <5 years, underlying cardiovascular disease, neurological disorders, blood disease and liver disease were significantly associated with all severe outcomes of RSV disease (Table 7).

Table 7 Multivariable logistic regression analysis of risk factors for RSV and its severe outcomes in age group <5 years (RSV cases and deceased RSV cases: week 01/2009-20/2018; ICU admitted RSV cases and ventilated RSV cases: week 01/2013-20/2018 original sentinel hospitals, week 01/2015-20/2018 additional sentinel hospitals) [23]

	RSV case		ICU admitted RSV case		Ventilated RSV case		Deceased RSV case	
	OR	**95%-CI**	**OR**	**95%-CI**	**OR**	**95%-CI**	**OR**	**95%-CI**
Age group								
0-5 months	**20.29**	**18.37-22.41**	**2.39**	**1.45-3.94**			0.28	0.03-2.29
6 months-1 year	**4.59**	**4.16-5.06**	0.87	0.52-1.48			0.63	0.10-4.21
2-4 years *(reference group)*	1		1				1	
Gender								
Male	**0.85**	**0.80-0.89**						
Female *(reference group)*	1							
Season								
2009/10	**0.38**	**0.31-0.45**						
2010/11	0.93	0.82-1.07						
2011/12	0.90	0.79-1.02						
2012/13	**1.26**	**1.12-1.41**						
2013/14 *(reference group)*	1							
2014/15	**1.58**	**1.42-1.74**						
2015/16	**1.14**	**1.03-1.26**						
2016/17	**2.06**	**1.88-2.27**						
2017/18	**1.78**	**1.61-1.97**						
Medical condition								
Low birth weight (1000-2499 grams)	1.18	0.72-1.93	**6.77**	**1.28-35.71**	**6.44**	**1.56-26.55**		
Preterm newborn (28-37 weeks)	1.43	0.92-2.24	**6.71**	**2.19-20.61**	**3.91**	**1.20-12.81**		
Respiratory and cardiovascular disorder specific to the perinatal period	**1.32**	**1.11-1.57**	**4.97**	**3.36-7.34**	**8.82**	**5.23-14.89**		
Congenital malformation of the heart	**0.69**	**0.56-0.85**	**3.65**	**1.90-7.02**	**3.85**	**1.63-9.13**	2.54	0.26-24.78
Congenital malformation of the great vessels	**0.38**	**0.26-0.58**	**3.50**	**1.10-11.18**	1.87	0.46-7.68		
Congenital defect originating in perinatal period	**0.41**	**0.31-0.55**	**4.07**	**1.71-9.70**	**3.30**	**1.05-10.34**	2.61	0.23-29.68

Down syndrome			2.61	0.93-7.31				
Cystic fibrosis	0.26	0.06-1.13			**35.13**	**1.76-700.59**		
Vitamin D deficiency					9.02	0.88-92.32		
Asthma	**0.40**	**0.30-0.53**						
Chronic pulmonary disease (excl. asthma and COPD)					3.67	0.69-19.46	**12.58**	**1.13-140.15**
Cardiovascular disease			**5.19**	**2.77-9.72**	**5.96**	**2.71-13.08**	**9.42**	**1.46-60.82**
Neurological disorders	**0.52**	**0.43-0.62**	**6.48**	**3.76-11.18**	**4.43**	**2.05-9.56**	**21.70**	**4.98-94.51**
Blood disease	**0.60**	**0.48-0.75**	**3.67**	**1.98-6.79**	**8.22**	**4.13-16.36**	**12.17**	**2.23-66.26**
Liver disease			**14.99**	**1.49-150.82**	**13.70**	**1.81-103.80**	**170.86**	**20.54-1421.11**
Cancer	0.60	0.17-2.07						

Statistically significant results appear in bold.

3.2.2.2 Risk factors for RSV and its severe outcomes in age group >=5 years

In multivariable analysis, among SARI cases aged >=5 years, the age group 5-64 years, the seasons 2016/17 and 2017/18, underlying congenital defect originating in perinatal period, cystic fibrosis, vitamin D deficiency and chronic pulmonary disease were significantly associated with an increased risk of being diagnosed with RSV. Among RSV cases aged >=5 years, the age group >=65 years was significantly associated with an increased risk of death. Underlying blood disease was significantly associated with all severe outcomes of RSV disease (Table 8).

Table 8 Multivariable logistic regression analysis of risk factors for RSV and its severe outcomes in age group >=5 years (RSV cases and deceased RSV cases: week 01/2009-20/2018; ICU admitted RSV cases and ventilated RSV cases: week 01/2013-20/2018 original sentinel hospitals, week 01/2015-20/2018 additional sentinel hospitals) [23]

	RSV case		ICU admitted RSV case		Ventilated RSV case		Deceased RSV case	
	OR	**95%-CI**	**OR**	**95%-CI**	**OR**	**95%-CI**	**OR**	**95%-CI**
Age group								
5-64 years *(reference group)*	1						1	
>=65 years	**0.53**	**0.39-0.71**					**5.01**	**1.31-19.15**
Season								
2009/10	0.60	0.17-2.11						
2010/11	1.29	0.52-3.21						
2011/12	1.65	0.73-3.73						
2012/13	**2.74**	**1.38-5.45**						
2013/14 *(reference group)*	1							
2014/15	**2.15**	**1.12-4.15**						
2015/16	1.71	0.87-3.39						
2016/17	**4.41**	**2.43-7.99**						
2017/18	**8.51**	**4.78-15.15**						
Medical condition								
Congenital defect originating in perinatal period	**3.74**	**1.19-11.76**						
Cystic fibrosis	**13.40**	**5.83-30.78**						
Vitamin D deficiency	**2.57**	**1.12-5.93**						
Asthma	1.73	0.96-3.12						
Chronic obstructive pulmonary disease (COPD)	0.75	0.50-1.11						
Chronic pulmonary disease (excl. asthma and COPD)	**2.04**	**1.23-3.38**						
Cardiovascular disease	**0.71**	**0.53-0.96**						
Blood disease			**4.38**	**1.56-12.27**	**3.40**	**1.22-9.50**	**7.17**	**1.31-19.15**
Renal failure	0.77	0.56-1.06	**2.27**	**1.13-4.55**				

Statistically significant results appear in bold.

4 Discussion

Using ICD-10-based outpatient surveillance data, age groups at high risk of RSV were identified, seasonality of RSV in Germany was described, and could be confirmed by data from the virological surveillance system. RSV specific ICD-10 codes had poor sensitivity and high specificity for the identification of laboratory-confirmed RSV infections in primary care. In young children within RSV seasons, two combinations of RSV specific and general ALRI ICD-10 codes increased the sensitivity without decreasing the specificity much [24]. Using ICD-10-based inpatient surveillance data, risk factors for being diagnosed with RSV disease and severe outcomes of RSV disease were identified in hospitalized SARI patients [23].

The described RSV epidemiology based on ICD-10 and virological data showed common findings like the high number of RSV cases among young children, higher number of RSV cases among young boys than young girls [24], and the strongest RSV season 2016/17 within the study period. These findings also correspond with those reported in previous studies [3, 4].

The RSV season based on SEED^{ARE} data began earlier than based on virological data. Thus, the ICD-10-based outpatient syndromic surveillance may provide earlier warning of RSV spread compared to the traditional virological surveillance [24].

In the present study, RSV specific ICD-10 codes were less sensitive for the identification of laboratory-confirmed RSV cases. There are currently no Coding Guidelines in primary care in Germany [25]. Laboratory diagnostic tests do not have to be performed for every suspected RSV infection in primary care in Germany. Even if testing is performed, an ICD-10 code diagnosis will possibly not be recoded when laboratory findings become available after the medical consultation a few days later. Thus, suspected and also laboratory-confirmed RSV infections may be encoded with general ARI ICD-10 codes. RSV specific ICD-10 codes were probably more likely to be encoded for young children during RSV seasons since RSV infection is more common in this group and during this time period. Thus, the combination of RSV specific and the general ALRI ICD-10 codes in children aged <5 years within RSV seasons achieved moderate sensitivities and high specificities [24].

The majority of RSV cases were aged <5 years in the present study. Thus, risk factors were investigated separately in two age groups <5 and >=5 years. To avoid confounding

effects, only variables with significant association with RSV or its severe outcomes in the univariable models were included in the multivariable models [23].

In the multivariable models for the age group <5 years, children in the first months of life were significantly more likely to be diagnosed with RSV among SARI cases, and they were more likely to be admitted to ICU among RSV cases. The findings are in line with the majority of reports that young age is a risk factor for hospitalization due to RSV [3, 4, 8] and that age below 3 months contributes to the increased severity of RSV disease [26]. Even though boys when compared to girls were more likely to be diagnosed with RSV [8], Grimwood et al. reported no association between being male and RSV [27]. In the present study, being female was a risk factor for being diagnosed with RSV, however gender did not play a role in developing severe outcomes of RSV disease [23]. Underlying chronic pulmonary or cardiovascular disease was known to be a risk factor for RSV [7, 8]. In the present study, children with underlying respiratory and cardiovascular disorders specific to the perinatal period were more likely to be diagnosed with RSV.

Low birth weight and prematurity were risk factors for ICU admission and application of ventilator support in RSV cases in the present study. Immature immune system and poorly developed airway of premature infants may contribute to this risk [7, 28]. Underlying congenital heart disease, congenital defect originating in perinatal period and cystic fibrosis were risk factors for ICU admission or application of ventilator support in RSV cases. These findings are in accordance with those reported in previous studies that among infants, underlying congenital heart disease increases severity of hospitalized RSV [29, 30], and RSV infection is more severe in those with underlying cystic fibrosis [7, 31]. Underlying neurological disorders, blood disease, and liver disease have been rarely investigated as possible risk factors for RSV or its severe outcomes in the literature. In the present study, they contributed to the severe outcomes of RSV disease among young children [23].

In the age group >=5 years, in SARI cases, older adults were less likely to be diagnosed with RSV, however, in RSV cases, they were more likely to die. Gender was not associated with RSV or its severe outcomes. The results regarding vitamin D deficiency are in agreement with findings of the previous studies that vitamin D may protect against ALRI due to RSV [32], but vitamin D deficiency may not be associated the increased severity of RSV [23, 33].

This work has some limitations. My analysis was based on ICD-10 code data. The RSV coding behavior of physicians may vary during and out of RSV seasons, based on use of laboratory diagnostics, age of patient, and level of coding awareness. The differences in coding behavior may lead to information bias. However, the evaluation of the accuracy of ICD-10 codes was exactly one of the objectives of my thesis. My analysis was based on anonymized data. According to practice-ID, age, gender, consultation date and sampling date alone, more than half of the respiratory specimens could not be matched with medical consultations based on SEED^{ARE} one to one, and were excluded for the evaluation of sensitivity and specificity of RSV specific ICD-10 codes which might lead to selection bias [24]. Based on the hospitalization data of ICOSARI, socio-demographic and environmental information of the cases could not be captured. Thus, underlying medical conditions, socio-demographic and environmental factors could not be evaluated in one model, which limited a comprehensive understanding of the risk factors for RSV and its severe outcomes. Further, no data were available to identify any children who had received palivizumab which would reduce the strength of association with risk factors. RSV is also a common pathogen of ARI in older adults. The results show among those aged >=65 years, that the proportion of RSV cases in SARI cases was lower than that reported in literature [34]. The data suggest that in elderly SARI patients, RSV testing might be less frequently carried out. Therefore, RSV could be underestimated in older adults. Although the sample size of the study population and RSV cases was large, the number of deceased RSV cases and RSV cases with some underlying medical conditions was small which may lead to sparse data bias. However, few other studies were large enough to look into the risk of death, whereas the approach using ICD-10-based surveillance data, despite this limitation, allowed analysis of deceased RSV cases [23].

In summary, the described RSV epidemiology based on ICD-10 and virological data showed similar age, gender and time distribution of RSV disease. RSV specific ICD-10 code data may provide earlier warning of RSV spread compared to virological data. Therefore, RSV specific ICD-10 codes are appropriate for RSV surveillance. However, in primary care, RSV specific ICD-10 code diagnosis was less sensitive, and relying on RSV specific ICD-10 codes alone, the actual number of RSV diseases will be underestimated. When establishing an ICD-10-based RSV surveillance system in young children in primary care, an extended ICD-10-based RSV case definition using the general ALRI ICD-10 codes may better capture the true RSV disease burden. Further investigations

are required to validate the use of the combinations of ICD-10 codes in RSV surveillance systems [24].

Using ICD-10-based hospital surveillance data allows identifying and monitoring risk factors for being diagnosed with RSV and severe outcomes of RSV disease. The findings will contribute to the development of a baseline of disease frequencies and burden of diseases as well as severity of cases for planning and evaluation of the RSV vaccination strategies and evaluation of the vaccination impact in the future, in particular on the target groups. Further studies regarding risk factors for RSV are needed with the focus on the underlying medical conditions showing inconsistent findings compared with the literature with consideration of socio-demographic and environmental factors [23].

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Affidavit

Eidesstattliche Versicherung

„Ich, Wei Cai, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Evaluation of using ICD-10 code data for RSV surveillance and identification of risk factors for RSV disease / Evaluation von Verwendung der ICD-10 Code Daten für RSV Surveillance und Identifikation von Risikofaktoren für RSV-Erkrankung“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

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Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Erstbetreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

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Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Wei Cai hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: **Cai W**, Tolksdorf K, Hirve S, Schuler E, Zhang W, Haas W, Buda S. Evaluation of using ICD-10 code data for respiratory syncytial virus surveillance. Influenza Other Respi Viruses. 2019;00:1-8.

Beitrag im Einzelnen: Entwicklung der Fragestellungen und des Studienprotokolls, Datenanalyse, Ausarbeitung und Darstellung der Studienergebnisse (inkl. aller Tabellen und Abbildungen), Erstellung des Entwurfs der Publikation und Überarbeitung des Entwurfs

Publikation 2: **Cai W**, Buda S, Schuler E, Hirve S, Zhang W, Haas W. Risk factors for hospitalized respiratory syncytial virus disease and its severe outcomes. Influenza Other Respi Viruses. 2020;00:1–13.

Beitrag im Einzelnen: Entwicklung der Fragestellungen und des Studienprotokolls, Datenanalyse, Ausarbeitung und Darstellung der Studienergebnisse (inkl. aller Tabellen und Abbildungen), Erstellung des Entwurfs der Publikation und Überarbeitung des Entwurfs

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Excerpt of the journal summary list (Publication 1)

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI
Selected Categories: **"INFECTIOUS DISEASES"** Selected Category Scheme: WoS
Gesamtanzahl: 88 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	LANCET INFECTIOUS DISEASES	20,494	25.148	0.067280
2	Lancet HIV	1,476	11.355	0.007950
3	CLINICAL INFECTIOUS DISEASES	61,618	9.117	0.120010
4	EMERGING INFECTIOUS DISEASES	29,657	7.422	0.057980
5	Eurosurveillance	8,482	7.127	0.031200
6	INFECTIOUS DISEASE CLINICS OF NORTH AMERICA	2,503	5.449	0.005170
7	CLINICAL MICROBIOLOGY AND INFECTION	15,983	5.394	0.039650
8	JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY	29,292	5.217	0.050730
9	JOURNAL OF INFECTIOUS DISEASES	45,662	5.186	0.075270
10	Journal of the International AIDS Society	3,638	5.131	0.013920
11	AIDS	20,578	4.914	0.038030
12	INTERNATIONAL JOURNAL OF HYGIENE AND ENVIRONMENTAL HEALTH	4,282	4.848	0.006360
13	Current HIV/AIDS Reports	1,490	4.710	0.004890
14	JOURNAL OF INFECTION	6,636	4.603	0.014730
15	Travel Medicine and Infectious Disease	1,230	4.450	0.003610
16	Current Opinion in HIV and AIDS	2,266	4.409	0.008060
17	ACS Infectious Diseases	749	4.325	0.003090
18	INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS	10,395	4.253	0.016630

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
19	JOURNAL OF VIRAL HEPATITIS	4,846	4.237	0.010070
20	JAIDS-JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES	14,668	4.116	0.033010
21	AIDS PATIENT CARE AND STDS	3,622	4.041	0.006760
22	Virulence	2,944	3.947	0.008450
23	CURRENT OPINION IN INFECTIOUS DISEASES	3,582	3.782	0.008230
24	Antimicrobial Resistance and Infection Control	820	3.568	0.003260
25	Transboundary and Emerging Diseases	2,441	3.504	0.005680
26	Infection and Drug Resistance	640	3.443	0.002160
27	Epidemics	576	3.364	0.002410
28	JOURNAL OF HOSPITAL INFECTION	7,523	3.354	0.010450
29	SEXUALLY TRANSMITTED INFECTIONS	4,769	3.346	0.009050
30	INFECTION AND IMMUNITY	46,798	3.256	0.034450
31	Open Forum Infectious Diseases	1,598	3.240	0.009070
32	INTERNATIONAL JOURNAL OF INFECTIOUS DISEASES	6,424	3.202	0.015340
33	INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY	10,374	3.084	0.019450
34	Influenza and Other Respiratory Viruses	1,589	2.954	0.006130
35	HIV MEDICINE	2,581	2.932	0.006230
36	MICROBES AND INFECTION	6,655	2.924	0.006120
37	Clinical and Vaccine Immunology	5,741	2.872	0.011440
38	MALARIA JOURNAL	12,743	2.845	0.029220
39	MEDICAL MYCOLOGY	4,078	2.799	0.005660
40	AIDS REVIEWS	651	2.775	0.001430

Publication 1

Cai W, Tolksdorf K, Hirve S, Schuler E, Zhang W, Haas W, Buda S. Evaluation of using ICD-10 code data for respiratory syncytial virus surveillance. Influenza Other Respi Viruses. 2019;00:1-8. https://doi.org/10.1111/irv.12665

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ORIGINAL ARTICLE

WILEY

Evaluation of using ICD-10 code data for respiratory syncytial virus surveillance

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Abstract

Background: Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract infection (ALRI) in young children. ICD-10-based syndromic surveillance can transmit data rapidly in a standardized way.

Objectives: We investigated the use of RSV-specific ICD-10 codes for RSV surveillance.

Methods: We performed a retrospective descriptive data analysis based on existing ICD-10-based surveillance systems for ALRI in primary and secondary care and a linked virological surveillance in Germany. We described RSV epidemiology and compared the epidemiological findings based on ICD-10 and virological data. We calculated sensitivity and specificity of RSV-specific ICD-10 codes and in combination with ICD-10 codes for acute respiratory infections (ARI) for the identification of laboratory-confirmed RSV infections.

Results: Based on the ICD-10 and virological data, epidemiology of RSV was described, and common findings were found. The RSV-specific ICD-10 codes had poor sensitivity 6% (95%-CI: 3%-12%) and high specificity 99.8% (95%-CI: 99.6%-99.9%). In children <5 years and in RSV seasons, the sensitivities of RSV-specific ICD-10 codes combined with general ALRI ICD-10 codes J18.-, J20.- and with J12.-, J18.-, J20.-, J21.-, J22 were moderate (44%, 95%-CI: 30%-59%). The specificities of both combinations remained high (91%, 95%-CI: 86%-94%; 90%, 95%-CI: 85%-94%).

Conclusions: The use of RSV-specific ICD-10 codes may be a useful indicator to describe RSV epidemiology. However, RSV-specific ICD-10 codes underestimate the number of actual RSV infections. This can be overcome by combining RSV-specific and general ALRI ICD-10 codes. Further investigations are required to validate this approach in other settings.

KEYWORDS
epidemiology, ICD-10 code, respiratory syncytial virus, sensitivity, specificity, surveillance

1 | INTRODUCTION

Respiratory syncytial virus (RSV) is a worldwide distributed pathogen of acute respiratory infection (ARI) of all ages. In infants and young children, RSV is the most common cause of acute lower respiratory tract infection (ALRI) and a major cause of hospital admission for ALRI. Worldwide in 2015, 21.6-50.3 million RSV-associated ALRI episodes occurred in children younger than 5 years, with about 2.7-3.8 million hospital admissions.[1,2]

Currently, only passive immunization with palivizumab against RSV is available for children at high risk.[3] In 2015, the World Health Organization (WHO) Product Development for Vaccines Advisory Committee highlighted the development of safe and efficacious RSV vaccines for global use. Several novel RSV vaccines have shown promising results in clinical trials and are expected to enter the market by 2025.[4,5] The planning of future RSV vaccination strategies and the evaluation of RSV vaccination impact rely on timely RSV epidemiological data and long-term observation of RSV seasonality through RSV surveillance systems.

International Statistical Classification of Diseases and Related Health Problems (ICD) diagnosis codes have been used to describe the burden of respiratory diseases and the impact of vaccination.[6-9] ICD-based digital syndromic surveillance is a relatively novel surveillance practice, compared to the traditional surveillance. It can not only describe epidemiology of disease, but also capture and transmit data rapidly in a standardized and sustainable way at lower costs, and provide very early warning of potential public health threats.[10-12]

The Robert Koch Institute (RKI) established the 10th revision of ICD (ICD-10)-based digital syndromic surveillance systems for influenza and other ARI in primary and secondary care in Germany (Appendix S1). In primary care, general practitioners, internists, and pediatricians of sentinel practices report influenza and other ARI data voluntarily through a syndromic influenza surveillance system. This system has been linked with a virological surveillance and a sentinel electronic data collection system based on ICD-10 codes (SEED^{ARE}).[13] SEED^{ARE} was evaluated as a valid system for syndromic influenza surveillance.[14] In secondary care, an ICD-10 code-based surveillance system for severe acute respiratory infections (ICOSARI) has been implemented in cooperation with a private hospital network in Germany.[15]

Studies estimating validity of ICD diagnosis codes for the identification of laboratory-confirmed influenza have shown mixed results.[14,16-18] So far, few studies have looked at accuracy of RSV-specific ICD-10 diagnosis codes for the identification of true RSV infections. To our knowledge, only Pisesky et al[19] reported high sensitivity (97.9%, 95%-CI: 95.5%-99.2%) and specificity (99.6%, 95%-CI: 98.2%-99.8%) of RSV-specific ICD-10 codes for the identification of hospitalized RSV among children.

The aim of this study was to evaluate the use of RSV-specific ICD-10 diagnosis codes for RSV surveillance.

2 | METHODS

We performed a retrospective descriptive data analysis based on the data derived from ICD-10-based influenza and other ARI surveillance systems SEED^{ARE} and ICOSARI, and from the virological surveillance at the RKI. The SEED^{ARE} system has functioned since 2007, the virological surveillance since 2010, and ICOSARI since 2015. The datasets of ICOSARI for the years 2009 to 2014 were collected retrospectively. The Appendix S1 provides details on the surveillance participants, data collection methods, collected data, total number of collected data, and study period ([13-15], Appendix S1).

The SEED^{ARE} system was approved by the German Federal Commissioner for Data Protection and Freedom of Information, and the ICOSARI system by the RKI and HELIOS Kliniken GmbH data protection authority. As SEED^{ARE} and ICOSARI involved no interventions and the analysis was based on anonymized data only, no ethical clearance was required for them.[14,15] The virological surveillance activities were approved by the German Federal Commissioner for Data Protection and Freedom of Information and the Ethical Committee of the Charité, Universitätsmedizin, Berlin.

We defined a RSV-ICD-case based on SEED^{ARE} data as a medical consultation with any of the three RSV-specific ICD-10 code diagnoses (J12.1 RSV pneumonia, J20.5 acute bronchitis due to RSV, and J21.0 acute bronchiolitis due to RSV).[6] We defined a RSV-ICD-case based on ICOSARI data as a hospitalization with any of the three RSV-specific ICD-10 code diagnoses as primary discharge diagnosis. In the virological surveillance, we defined a confirmed-RSV-case as a by real-time reverse transcriptase polymerase chain reaction (rtRT-PCR) confirmed RSV sample. In each data source, a RSV season was defined as the weeks when cumulative number of RSV-ICD-cases or confirmed-RSV-cases exceeded 1.2% of total RSV-ICD-cases or confirmed-RSV-cases. One gap week below the threshold was allowed.[20,21]

We estimated number of RSV-ICD-cases and confirmed-RSV-cases by gender, age group (0-1, 2-4, 5-14, 15-34, 35-49, 50-59, ≥60 years), and calendar week based on each data source, respectively.

We identified the sentinel practices that participated in both SEED^{ARE} and the virological surveillance concurrently by practice-ID. We matched the medical consultations of SEED^{ARE} with virological samples by practice-ID, age, gender, consultation date, and sampling date. Only one-to-one matches were included for the further data evaluation. We calculated sensitivity of RSV-specific ICD-10 code diagnosis as proportion of RSV-ICD-cases among confirmed-RSV-cases, and specificity as proportion of non-RSV-ICD-cases among non-confirmed-RSV-cases of the identified practices. We calculated sensitivity and specificity of RSV-specific ICD-10 code diagnosis among young children, in RSV seasons, and combined with different general ARI ICD-10 codes J06.- acute upper respiratory infections of multiple and unspecified sites (J06, J06.0, J06.8, J06.9), J11.- influenza, virus not identified (J11, J11.0, J11.1, J11.8), J12.- viral pneumonia, not elsewhere classified (J12, J12.8, J12.9), J18.- pneumonia, organism unspecified (J18, J18.0, J18.8, J18.9), J20.- acute bronchitis (J20, J20.8, J20.9), J21.- acute bronchiolitis (J21, J21.8, J21.9), J22 unspecified ALRI, and B34.9 unspecified viral infection, respectively.[6] The sensitivities and specificities were calculated with 95% confidence interval (95%-CI). Additionally, we compared RSV-ICD-cases with confirmed-RSV-cases of the identified practices by calendar week.

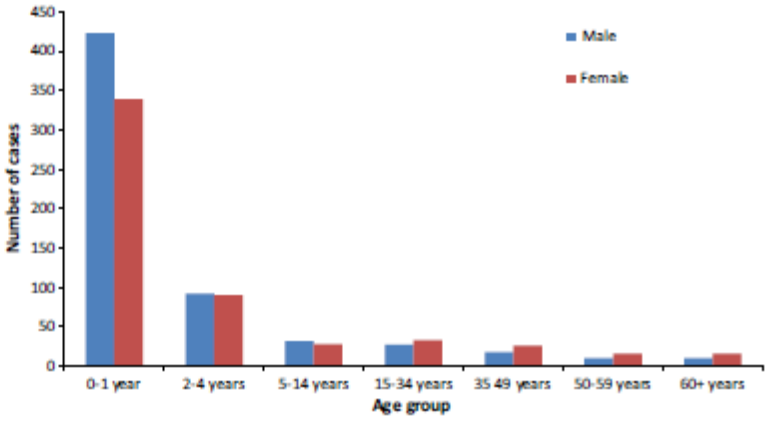

FIGURE 1 Number of RSV-ICD-cases by age group and gender based on SEED^{ARE}, week 40/2007-13/2017

We used Stata (version 15) and MICROSOFT EXCEL 2010 for the data analysis.

3 | RESULTS

3.1 | Primary care

3.1.1 | Descriptive analysis of RSV-ICD-cases based on SEED^{ARE} data

A total of 1165 RSV-ICD-cases were identified from the SEED^{ARE} database from week 40/2007-13/2017. Among those, 338 (29%) were diagnosed with J12.1, 432 (37%) with J20.5, and 395 (34%) with J21.0. The proportion of RSV-ICD-cases among all ARI-ICD-cases was 0.1%.

About two-thirds (765; 66%) of RSV-ICD-cases were children aged <2 years. The number of RSV-ICD-cases declined rapidly from 2 years of age and remained at a constantly low level from 5 years of age onwards. Under 2 years of age, the number of RSV-ICD-cases was higher in boys (423) than in girls (339; Figure 1).

The cumulative number (88) of the RSV-ICD-cases within the observed 10-year period peaked in the 8th calendar week, and the proportion (0.3%) of RSV-ICD-cases among all ARI-ICD-cases peaked in the 2nd calendar week. The RSV season on average was from 41st to 16th calendar week with the season length of 28 weeks. Within the RSV seasons, 92% (1075) RSV-ICD-cases were captured.

3.1.2 | Descriptive analysis of confirmed-RSV-cases based on virological surveillance data

From week 40/2010-18/2017, 1785 (8%) respiratory specimens of ARI or influenza-like illness (ILI) patients were RSV positive.

The highest RSV positive rate (25%; 659) was among children aged <2 years. The RSV positive rate decreased from 2 years of age, reached the lowest level in the age group 15-34 years (2%; 98), then increased slightly again, and reached 6% (145) at the age of 60 years and older. Under 2 years of age, the RSV-positive rate was higher among boys (25%; 378) than girls (24%; 270; Figure 2).

The cumulative number (143) of confirmed-RSV-cases peaked in the 6th calendar week, and the RSV positive rate (18%) peaked in the 52nd calendar week. The RSV season on average was from 48th to 15th calendar week with the season length of 20 weeks. Within the RSV seasons, 94% (1671) confirmed-RSV-cases were captured.

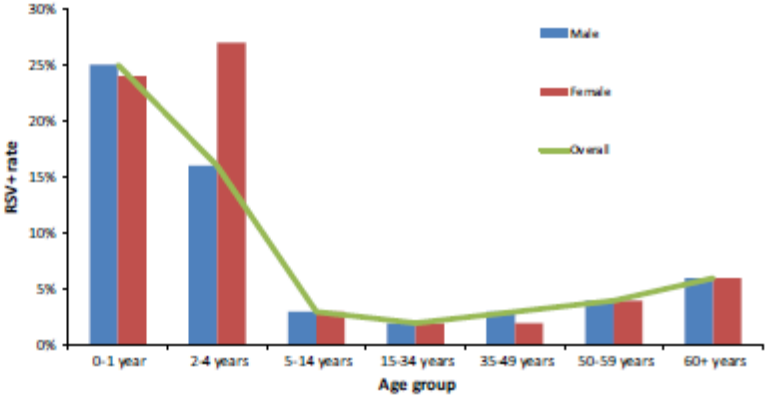

FIGURE 2 RSV-positive rate by age group and gender based on virological surveillance, week 40/2010-18/2017

3.2 | Integration of RSV data of practices participated in SEED^{ARE} and virological surveillance

Forty-eight sentinel practices participated in both SEED^{ARE} and the virological surveillance from week 40/2010-13/2017. In total, 5589 respiratory specimens of the 48 practices were tested for RSV. Of those, 400 (7%) were RSV positive, and 2624 (47%) could be matched with the medical consultations based on SEED^{ARE} one to one (Figure 3).

Overall, the sensitivity of RSV-specific ICD-10 code diagnosis was 6% (95%-CI: 3%-12%), and the specificity was 99.8% (95%-CI: 99.6%-99.9%). The sensitivity (16%, 95%-CI: 7%-29%) increased among children aged <5 years and during the RSV seasons based on the virological data (48th–15th calendar week), and the specificity (99.5%, 95-CI: 97.5%-99.9%) remained high. In children aged <5 years and in RSV seasons, the sensitivities of RSV-specific ICD-10 codes combined with general ALRI ICD-10 codes J18.-, J20.-, and with J12.-, J18.-, J20.-, J21.-, J22 both reached 44% (95%-CI: 30%-59%), and the specificities of the two combinations were still at a high level (91%, 95%-CI: 86%-94%; 90%, 95%-CI: 85%-94%). The sensitivity of RSV-specific ICD-10 codes combined with all general ARI ICD-10 codes was 90% (95%-CI: 78%-97%), whereas the specificity was 16% (95%-CI: 11%-21%; Table 1).

Figures 4 and 5 indicate number and proportion of RSV-ICD-cases based on the SEED^{ARE} and confirmed-RSV-cases based on the virological surveillance in the 48 practices by calendar week, respectively. The trends of the curves were similar.

3.3 | Secondary care

3.3.1 | Descriptive analysis of RSV-ICD-cases based on ICOSARI data

Among 1 417 700 respiratory disease, hospitalizations from week 01/2009-15/2017, 7345 (0.5%) were hospitalizations with any of the RSV-specific ICD-10 codes as primary or secondary discharge diagnosis, and 3154 (0.2%) as admission diagnosis. Of the 7345 RSV hospitalizations, 6918 (94%) were with RSV-specific ICD-10 codes as primary discharge diagnosis. Of the three RSV-specific ICD-10 codes, J21.0 was most frequently diagnosed as primary discharge (2705; 39%) and also admission diagnosis (1679; 53%).

Of the 6918 RSV-ICD-cases, 93% (6415) were children aged <2 years. The number of RSV-ICD-cases declined rapidly from 2 years of age. From 5 years of age, only a few RSV-ICD-cases were identified in each age group. In the age group 60 years and older, the number (32) of RSV-ICD-cases rose slightly. Under 2 years of age, number of RSV-ICD-cases was higher among boys (3623) than girls (2792; Figure 6).

The cumulative number (535) of RSV-ICD-cases peaked in the 5th calendar week, and the proportion (2.1%) peaked in the 52nd calendar week. The RSV season on average was from 48th to 16th calendar week with the season length of 21 weeks. Within the RSV seasons, 93% (6444) RSV-ICD-cases were captured.

4 | DISCUSSION

Using ICD-10-based surveillance, we identified age groups under high risk of RSV, and successfully described general trends and seasonality of RSV in primary and secondary care in Germany, as confirmed by data from the virological surveillance system. In primary care, RSV-specific ICD-10 codes had poor sensitivity and high specificity for the identification of laboratory-confirmed RSV infections. In young children, two combinations of RSV-specific ICD-10 codes with general ALRI ICD-10 codes increased the sensitivity without decreasing the specificity much.

The described RSV epidemiology based on ICD-10 code and virological data showed many common findings. Especially, high number of RSV cases among young children, and higher number of RSV cases among young boys than young girls were found in ICD-10 and

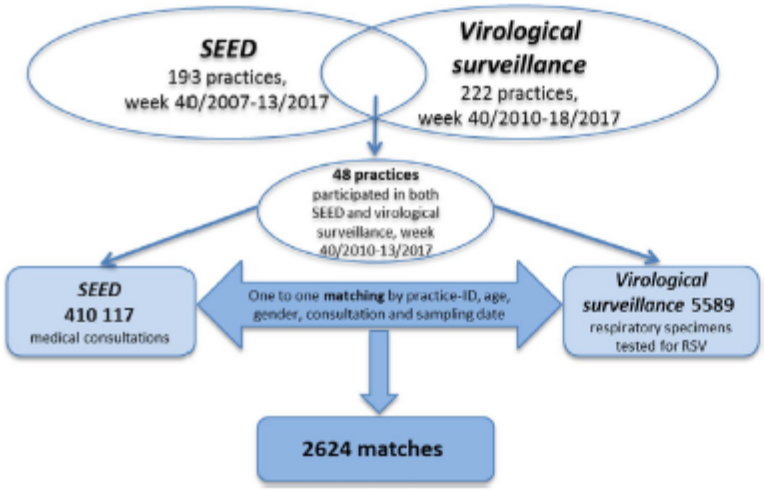

FIGURE 3 Integration of RSV data of practices participated in both SEED^{ARE} and virological surveillance, week 40/2010-13/2017

TABLE 1 Sensitivities and specificities of RSV-specific ICD-10 code diagnosis combined with different general ARI ICD-10 codes of the practices participated in both SEED^{ARE} and virological surveillance, week 40/2010-13/2017

	Sensitivity		Specificity	
	%	95%-CI	%	95%-CI
RSV codes[a]	6	3-12	99.8	99.6-99.9
<2 y of age				
RSV codes	8	2-22	99.4	95.6-99.9
<5 y of age				
RSV codes	14	6-26	99.6	98-99.9
In RSV seasons[b]				
RSV codes	7	3-12	99.8	99.5-99.9
<5 y of age and in RSV seasons				
RSV codes	16	7-29	99.5	98-99.5
RSV codes + J06.-[c]	48	34-63	62	55-68
RSV codes + J11.-[d]	30	18-45	75	68-80
RSV codes + J12.-[e]	16	7-29	99.5	98-99.9
RSV codes + J18.-[f]	30	18-45	98	95-99
RSV codes + J20.-[g]	30	18-45	92	88-95
RSV codes + J21.-[h]	16	7-29	99.5	98-99.9
RSV codes + J22	16	7-29	99	97-99.9
RSV codes + B34.9	28	16-42	80	74-85
RSV codes + J18.-, J20.-	44	30-59	91	86-94
RSV codes + J18.-, J20.-, B34.9	56	41-70	72	65-77
RSV codes + J11.-, J18.-, J20.-, B34.9	62	47-75	48	42-55
RSV codes + J12.-, J18.-, J20.-, J21.-, J22	44	30-59	90	85-94
RSV codes + all general ARI codes[i]	90	78-97	16	11-21

[a]RSV codes: RSV-specific ICD-10 codes J12.1, J20.5, J21.0.
[b]RSV season: 48th-15th calendar week.
[c]J06.-: J06, J06.0, J06.8, J06.9.
[d]J11.-: J11, J11.0, J11.1, J11.8.
[e]J12.-: J12, J12.8, J12.9.
[f]J18.-: J18, J18.0, J18.8, J18.9.
[g]J20.-: J20, J20.8, J20.9.
[h]J21.-: J21, J21.8, J21.9.
[i]All general ARI codes: J06, J06.0, J06.8, J06.9, J11, J11.0, J11.1, J11.8, J12, J12.8, J12.9, J18, J18.0, J18.8, J18.9, J20, J20.8, J20.9, J21, J21.8, J21.9, J22, B34.9.

also in virological data sources. These findings are also in accordance with those reported in the literature.[1,2,22,25]

In the present study, the proportion of young children among all RSV-ICD-cases was higher in secondary care based on ICOSARI than in primary care based on SEED^{ARE} data. This is in agreement with the clinical observation that RSV infection is normally more serious in young children and is a major cause of hospital admission in this group.[1,2] Bronchiolitis is a very severe manifestation of RSV disease mainly affecting young children, whereas bronchitis is more common in older children and adults.[24,25] Of the three RSV-specific ICD-10 codes, J21.0 (acute bronchiolitis due to RSV) was most frequently diagnosed in secondary care based on ICOSARI and J20.5 (acute bronchitis due to RSV) in primary care based on SEED^{ARE}.

Based on the three data sources, the RSV season onset ranged from mid-October to end-November, the season offset was in mid-April, and the peak of season ranged from end-January to mid-February in Germany. The RSV season length ranged from 20 to 28 weeks. The RSV seasons captured most of the RSV cases. RSV season onset, offset, peak week, and season length based on ICOSARI and virological surveillance were similar. Based on SEED^{ARE} outpatient surveillance, the season began earlier. The outpatient syndromic surveillance may provide earlier warning of RSV spread compared to the ICOSARI inpatient syndromic surveillance and the traditional virological surveillance. The RSV seasonality based on present study correlates well with the literature that the peak of RSV season is in winter months in Germany and areas with similar climate in the northern hemisphere.[26-28] The median length of RSV seasons in the present study was longer than the median length of RSV seasons in the 15 European countries.[21]

The similar RSV seasonality based on ICD-10 data in secondary care and virological data in primary care, and the similar RSV trends based on ICD-10 and virological data of the practices participated in both SEED^{ARE} and virological surveillance indicated that the RSV-specific ICD-10 code data reflected the true temporal distribution of RSV infection.

We found that RSV-specific ICD-10 codes were less sensitive and highly specific for the identification of laboratory-confirmed RSV infections in primary care. Low sensitivity of the ICD-10 codes was also reported for influenza.[16-18] In Germany, laboratory diagnostic tests are not always performed for suspected RSV infections in primary care. Even if testing is performed, an ICD-10 code diagnosis will probably no longer be recoded when laboratory findings are only available in the practice a few days later after the medical consultation. Therefore, suspected and also laboratory-confirmed RSV infections may be encoded with general ARI ICD-10 codes. These could be the reasons why most of the laboratory-confirmed RSV cases were not encoded with RSV-specific ICD-10 codes in the sentinel practices which participated in both the SEED^{ARE} and virological surveillance in the present study. In preparation for the present study, the RKI performed a survey to explore RSV coding behavior in primary care in Germany. The results of the survey are in line with the explanations above (unpublished data).

In children aged <5 years and in RSV seasons, the sensitivity of RSV-specific ICD-10 codes grew more than twofold, and the specificity remained high. Physicians were probably more likely to encode with RSV-specific ICD-10 codes for young children and in RSV seasons since RSV is more common in this group and during this time period. In the present study, we tried estimating the sensitivities and specificities of RSV-specific ICD-10 codes combined with different general ARI ICD-10 codes. RSV-specific ICD-10 codes combined with two groups of general ALRI ICD-10 codes achieved moderate sensitives and high specificities. The high sensitivity of RSV-specific

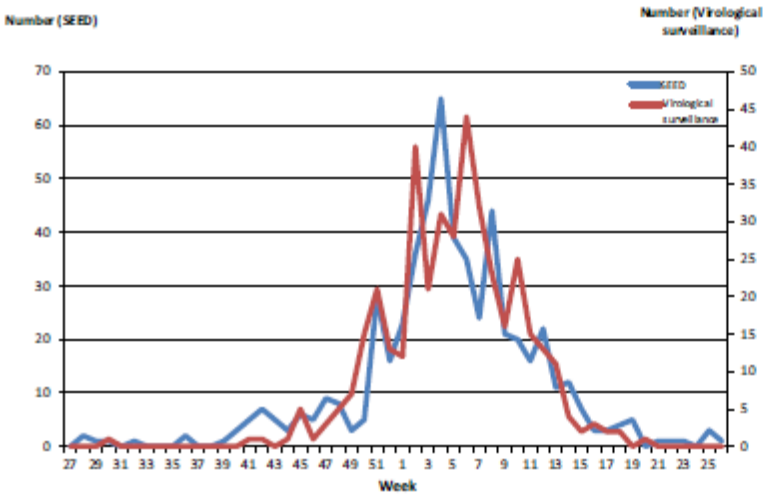

FIGURE 4 Cumulative number of RSV-ICD-cases based on SEED[ARE] and cumulative number of confirmed-RSV-cases based on virological surveillance by calendar week in the practices participated in both SEED[ARE] and virological surveillance, week 40/2010-18/2017

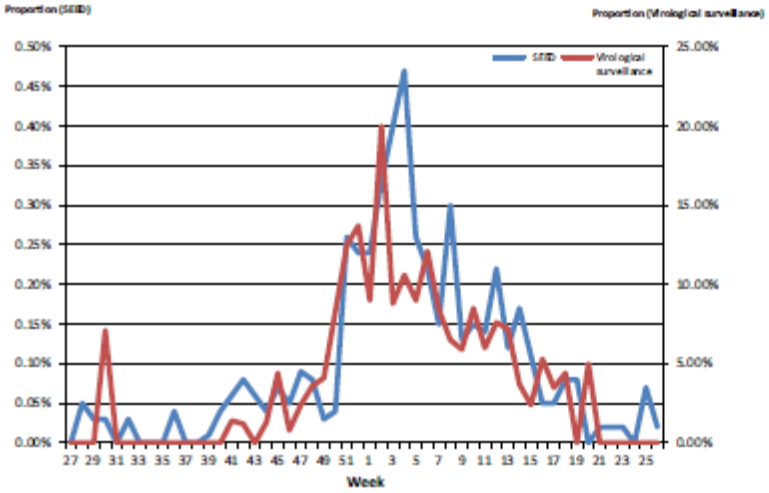

FIGURE 5 Proportion of RSV-ICD-cases based on SEED[ARE] and RSV positive rate based on virological surveillance by calendar week in the practices participated in both SEED[ARE] and virological surveillance, week 40/2010-18/2017

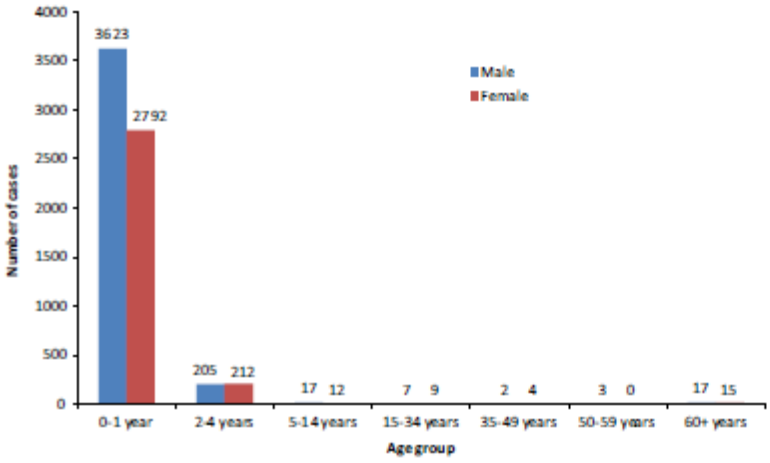

FIGURE 6 Number on RSV-ICD-cases by age group and gender based on ICOSARI, week 01/2009-15/2017

ICD-10 codes combined with all general ARI ICD-10 codes suggests that in addition to RSV-specific ICD-10 codes, most laboratory-confirmed RSV infections were diagnosed with general ARI ICD-10 codes. Thus, the misclassification related to inaccurate labeling of RSV infections with other disease- or pathogen-specific ICD-10 codes was uncommon in the present study.

The present study has some limitations. The sensitivity and specificity of RSV-specific ICD-10 code diagnoses in secondary care could not be evaluated on a case by case basis since virological data of the ICOSARI network were not available for the present study. However, in the ICOSARI network, suspected RSV cases in young children were tested by rapid antigen detection tests and rtRT-PCR, and laboratory-confirmed RSV infections were encoded with RSV-specific ICD-10 codes. Although whether the testing and coding took place in a 100% frequency is not verified, these have been as a standard procedure in the pediatric units and the coding quality could have increased in recent years (personal communication). In addition, high validity has been reported in the literature for RSV-specific ICD-10 codes for the identification of hospitalized RSV among children.[19]

The RSV coding behavior of physicians in primary care may vary during and out of RSV season, based on use of laboratory diagnostics, age of patient, and level of coding awareness. The differences in coding behavior may lead to information bias. The number of confirmed-RSV-cases and RSV-ICD-cases increased slightly among older adults based on virological as well as ICOSARI data, and it remained at a low level based on SEED^{ARE}. The RSV infection normally goes unrecognized with milder symptoms among adults; however, it is a common pathogen of ARI in older adults and can lead to severe disease.[29,50] Therefore, the RSV infections were probably underestimated among older adults in SEED^{ARE}. This could be another limitation. However, the evaluation of the accuracy of ICD-10 codes was exactly the objective of the present study due to the potential information bias.

The present study was based on anonymized data. According to practice-ID, age, gender, consultation date, and sampling date alone, more than half of the virological samples could not be matched to medical consultations one to one and were excluded for the evaluation of sensitivity and specificity of RSV-specific ICD-10 codes which might lead to selection bias. However, the probability of the selection bias was low since no conspicuous deviations were found between the matched and the excluded virological data (data not shown).

5 | CONCLUSIONS

The use of RSV-specific ICD-10 code data may be a useful indicator to identify age groups under high risk of RSV, to monitor general trends, and to observe seasonality of RSV. The RSV epidemiology based on ICD-10 code data from different data sources and virological data showed similar age and sex distribution, percent positivity, and seasonality patterns. Therefore, RSV-specific ICD-10 codes are appropriate for RSV surveillance. However, in primary care, RSV-specific ICD-10 code diagnosis was less sensitive, and relying on RSV-specific ICD-10 codes alone will underestimate the actual number of RSV infections. RSV-specific ICD-10 codes combined with the general ALRI ICD-10 codes J18.-, J20-., and with J12.-, J18.-, J20.-, J21.-, J22 achieved moderate sensitives and high specificities, respectively. Thus, when establishing an ICD-10-based digital RSV surveillance system in young children, an extended ICD-10-based RSV case definition using the two combinations of ICD-10 codes seems to better capture the true RSV disease burden. Further investigations are required to validate the use of the two combinations of ICD-10 codes in RSV surveillance systems in other countries as the RSV coding behavior may differ in different countries, to find out an even better combination of ICD-10 codes for the identification of RSV infections in primary care, and to evaluate the use of RSV-specific ICD-10 codes in secondary care.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Wei Cai, Silke Buda, Walter Haas, Siddhivinayak Hirve, and Wenqing Zhang were involved in designing the study. Kristin Tolksdorf, Silke Buda, and Ekkehard Schuler participated in the collection of ICOSARI data. Wei Cai analyzed the data, and Kristin Tolksdorf helped analyze the data. Wei Cai drafted the manuscript. All authors reviewed and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Excerpt of the journal summary list (Publication 2)

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **"INFECTIOUS DISEASES"** Selected Category Scheme: WoS
Gesamtanzahl: 89 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	LANCET INFECTIOUS DISEASES	23,088	27.516	0.073350
2	Lancet HIV	2,417	14.753	0.014270
3	CLINICAL INFECTIOUS DISEASES	64,031	9.055	0.119010
4	Eurosurveillance	9,131	7.421	0.031660
5	EMERGING INFECTIOUS DISEASES	30,311	7.185	0.059420
6	CLINICAL MICROBIOLOGY AND INFECTION	17,929	6.425	0.036730
7	Journal of the International AIDS Society	4,530	5.152	0.018770
8	JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY	30,927	5.113	0.048620
9	JOURNAL OF INFECTION	6,946	5.099	0.014410
10	JOURNAL OF INFECTIOUS DISEASES	45,452	5.045	0.076010
11	ACS Infectious Diseases	1,459	4.911	0.005600
12	Travel Medicine and Infectious Disease	1,576	4.868	0.004660
13	Virulence	3,557	4.775	0.009120
14	INFECTIOUS DISEASE CLINICS OF NORTH AMERICA	2,766	4.757	0.005160
15	INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS	11,529	4.615	0.017010
16	AIDS	19,276	4.499	0.038330
17	Current HIV/AIDS Reports	1,569	4.382	0.004860
18	INTERNATIONAL JOURNAL OF HYGIENE AND ENVIRONMENTAL HEALTH	4,852	4.379	0.007830

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
19	Current Opinion in HIV and AIDS	2,426	4.268	0.008530
20	JOURNAL OF TRAVEL MEDICINE	2,229	4.155	0.003410
21	JOURNAL OF VIRAL HEPATITIS	4,816	4.016	0.009640
22	JAIDS-JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES	14,479	3.863	0.037150
23	CURRENT OPINION IN INFECTIOUS DISEASES	3,631	3.752	0.007600
24	AIDS PATIENT CARE AND STDS	3,526	3.742	0.006900
25	HIV MEDICINE	2,660	3.734	0.006570
26	JOURNAL OF HOSPITAL INFECTION	7,963	3.704	0.010250
27	Transboundary and Emerging Diseases	3,321	3.554	0.007140
28	INTERNATIONAL JOURNAL OF INFECTIOUS DISEASES	7,119	3.538	0.016950
29	Open Forum Infectious Diseases	2,694	3.371	0.013970
30	SEXUALLY TRANSMITTED INFECTIONS	4,686	3.365	0.009490
31	Epidemics	806	3.239	0.003170
32	Clinical and Vaccine Immunology	5,772	3.233	0.010040
33	Antimicrobial Resistance and Infection Control	1,294	3.224	0.004910
34	INFECTION AND IMMUNITY	46,129	3.160	0.029050
35	Infectious Diseases of Poverty	1,284	3.123	0.005100
36	Influenza and Other Respiratory Viruses	2,044	3.094	0.006330
37	Ticks and Tick-Borne Diseases	2,693	3.055	0.006730
38	Infection and Drug Resistance	976	3.000	0.002730
39	INFECTION	3,607	2.927	0.006650

Publication 2

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ORIGINAL ARTICLE

WILEY

Risk factors for hospitalized respiratory syncytial virus disease and its severe outcomes

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Abstract

Introduction: Respiratory syncytial virus (RSV) is a major cause of hospital admission for acute lower respiratory tract infection in young children.

Objectives: We aimed to identify risk factors for hospitalized RSV disease and its severe outcomes.

Methods: We conducted a retrospective cohort study analyzing data of a ICD-10-code-based hospital surveillance for severe acute respiratory infections (SARI). Using univariable and multivariable logistic regression analysis, we assessed age-group, gender, season, and underlying medical conditions as possible risk factors for RSV and its severe outcomes including ICU admission, application of ventilator support, and death, respectively.

Results: Of the 413 552 patients hospitalized with SARI in the database, 8761 were diagnosed with RSV from week 01/2009 to 20/2018 with 97% (8521) aged <5 years. Among children aged <5 years, age-groups 0-5 months (OR: 20.29, 95% CI: 18.37-22.41) and 6 months-1 year (OR: 4.59, 95% CI: 4.16-5.06), and underlying respiratory and cardiovascular disorders specific to the perinatal period (OR: 1.32, 95% CI: 1.11-1.57) were risk factors for being diagnosed with RSV. Age-group 0-5 months (OR: 2.39, 95% CI: 1.45-3.94), low birth weight (OR: 6.77, 95% CI: 1.28-35.71), preterm newborn (OR: 6.71, 95% CI: 2.19-20.61), underlying respiratory and cardiovascular disorders specific to the perinatal period (OR: 4.97, 95% CI: 3.36-7.34), congenital malformation of the heart (OR: 3.65, 95% CI: 1.90-7.02), congenital malformation of the great vessels (OR: 3.50, 95% CI: 1.10-11.18), congenital defect originating in perinatal period (OR: 4.07, 95% CI: 1.71-9.70), cardiovascular disease (OR: 5.19, 95% CI: 2.77-9.72), neurological disorders (OR: 6.48, 95% CI: 3.76-11.18), blood disease (OR: 3.67, 95% CI: 1.98-6.79), and liver disease (OR: 14.99, 95% CI: 1.49-150.82) contributed to ICU admission in RSV cases.

Conclusions: Using ICD-10-based surveillance data allows to identify risk factors for hospitalized RSV disease and its severe outcomes, and quantify the risk in different age-groups.

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KEYWORDS
comorbidity, hospitalization, intensive care units, international classification of diseases, logistic models, respiratory syncytial virus, risk factors, ventilation

1 | INTRODUCTION

Respiratory syncytial virus (RSV) is a worldwide distributed pathogen of acute respiratory infection (ARI) of all ages. In infants and young children, RSV is the most common cause of acute lower respiratory tract infection (ALRI) and a major cause of hospital admission for ALRI. Worldwide, about 33 million RSV-associated ALRI episodes occurred in children younger than 5 years, and about 3 million were severe enough to necessitate hospital admission in 2015.[1,2] RSV has been found to be an important cause of viral infection requiring pediatric intensive care unit (ICU) admission and ventilator support, as well as a frequent course of death in young children.[3,4]

Currently, there are no licensed vaccines against RSV; only passive immunization with palivizumab is available for young children at high risk.[5] In 2015, the World Health Organization Product Development for Vaccines Advisory Committee highlighted the development of RSV vaccines. Several novel RSV vaccines and long-acting monoclonal antibodies have shown promising results in clinical trials and are expected to enter the market in a short-medium term.[6,7]

Risk groups of severe RSV will benefit most from the RSV immunization once RSV vaccines become available. So far, some studies indicated that besides some socio-demographic and environmental factors including being male, household crowding, and passive smoking, underlying medical conditions such as prematurity, congenital heart disease, and chronic pulmonary and cardiovascular diseases were associated with RSV disease.[8-10] Furthermore, certain underlying medical conditions predispose young children to severe RSV disease[9,11] which is likely to result in ICU admission with ventilator support and a higher risk of death.[12] However, to our knowledge, the risk of underlying medical conditions has not been assessed comprehensively with respect to risk for RSV and its severe outcomes, and studies have shown inconsistent results for some underlying medical conditions.[10]

The development of RSV vaccination strategies and the evaluation of the effects of RSV vaccination in the future rely on timely epidemiological data and long-term observation of epidemiological situation of severe RSV and risk factors for severe RSV through national and other large-scale RSV surveillance systems. The Robert Koch Institute (RKI) established an International Statistical Classification of Diseases, 10th revision (ICD-10)-code-based surveillance system for severe ARI (ICOSARI) in cooperation with a private hospital network in Germany in 2015. Data of respiratory hospitalizations have been collected through the ICOSARI.[13,14]

The aim of the present study was to identify risk factors, in particular underlying medical conditions as risk factors, for hospitalized RSV disease and its severe outcomes based on the ICD-10-code-based surveillance data.

1.1 | Methods

We performed a retrospective cohort study based on secondary data analysis of the ICOSARI database. The hospital network of ICOSARI includes 45 original sentinel hospitals, and additional 42 hospitals joined the hospital network after 2013. In 2015, 84 sentinel hospitals of ICOSARI located in 13 of the 16 federal states of Germany, covered 4.3% hospitals, and accounted for 5.9% of hospitalized patients in Germany. Since 2015, digital data of hospitalizations with any of respiratory ICD-10 code (chapter X: J00-J99)[15] as primary or secondary discharge diagnosis have been collected prospectively and updated weekly. For retrospective analysis, ICD-10 datasets of ICOSARI for the years 2009 to 2014 were collected. The collected data contain information on age, gender, admission and discharge date, primary and all secondary ICD-10 code discharge diagnoses, length of hospital and ICU stay (in days), length of ventilation (in hours), and discharge mode. Further detailed description of the ICOSARI methodology was published elsewhere.[15]

The ICOSARI system was approved by the RKI and HELIOS Kliniken GmbH data protection authorities. As ICOSARI involved no interventions and the analysis was based on anonymized data only, no ethical clearance was required for this study.[16]

We used the following case definitions:

- Severe ARI (SARI) case: any patient hospitalized with any of the ARI ICD-10 codes J09-J22 (J09-J11: influenza, J12-J18: pneumonia, J20: acute bronchitis, J21: acute bronchiolitis, J22: unspecified acute lower respiratory infection) as primary or secondary discharge diagnosis[15,16]; If a patient was readmitted to hospital, the patient would be counted again.
- RSV case: SARI case diagnosed with any of the RSV-specific ICD-10 codes (J12.1: RSV pneumonia, J20.5: acute bronchitis due to RSV, J21.0: acute bronchiolitis due to RSV) as primary or secondary discharge diagnosis.[15]
- ICU-admitted RSV case: RSV case ever admitted to an ICU during the hospital stay.
- Ventilated RSV case: ICU-admitted RSV case ever required ventilator support during the hospital stay.
- Deceased RSV case: RSV case died in hospital.

ICU admission, application of ventilator support, and death were considered markers of severe outcomes of hospitalized RSV disease.

Due to the possible inconsistent recording practices on ICU admission and application of ventilator support in the sentinel hospitals (personal communication), data on ICU admission and application of ventilator support from the original sentinel hospitals before 2013

and from the additional sentinel hospitals before 2015 were excluded from our data evaluation.

The underlying medical conditions evaluated in our study were neonatal disorders (disorder of newborn related to slow fetal growth and fetal malnutrition), extremely low birth weight (<1000 g), low birth weight (1000-2499 g), extreme immaturity of newborn (<28 weeks), preterm newborn (28-37 weeks), respiratory and cardiovascular disorder specific to the perinatal period (eg, intrauterine hypoxia, birth asphyxia, respiratory distress of newborn, congenital pneumonia, neonatal aspiration syndromes, interstitial emphysema, pulmonary hemorrhage), congenital disorders (congenital malformation of the heart, congenital malformation of the great vessels, congenital defect originating in perinatal period, Down syndrome, sickle-cell disorder, cystic fibrosis), other comorbidities (vitamin D deficiency, asthma, chronic obstructive pulmonary disease (COPD), chronic pulmonary disease (excl. asthma and COPD), diabetes, cardiovascular disease, neurological disorders, blood disease (eg, nutritional anemias, coagulation defects, purpura, and other hemorrhagic conditions), renal failure, liver disease, tuberculosis, cancer, HIV/AIDS), and pregnancy. The underlying medical conditions could be primary or secondary discharge diagnoses. The specific ICD-10 codes of the medical conditions chosen for our data evaluation are listed in Table 1, which were adapted from the Elixhauser and Fleming Comorbidity Indices.[16,17]

For descriptive data analysis, we described the number of total RSV cases, ICU-admitted RSV cases, ventilated RSV cases, and deceased RSV cases by age-group (0-5 months, 6 months-1 year, 2-4 years, 5-64 years, ≥65 years), gender, calendar week, and underlying medical condition, respectively. The mean and median length of hospital stay, ICU stay and ventilation, and discharge mode were investigated, respectively.

We carried out univariable and multivariable logistic regression analyses to assess age-group, gender, season, and underlying medical conditions as possible risk factors for being diagnosed with RSV among SARI cases, for ICU admission, application of ventilator support, and death among RSV cases, respectively. The univariable and multivariable logistic regression analyses were stratified in two age-groups <5 years and ≥5 years. Underlying neonatal disorders were only evaluated as possible risk factors in the age-group <5 years. Normally, relative risk (RR) should be calculated to measure the association between the exposure and the outcome in a cohort study. However, the odds ratios (OR) provides a reasonable approximation of the RR if the outcome is rare and occurs in less than 10% of the unexposed population.[18] Our data met this condition that RSV cases were rare among SARI cases and RSV cases with different severe outcomes were rare among total RSV cases. Therefore, the ORs could be interpreted as RRs in our cohort study. ORs were calculated and presented with 95% confidence interval (95% CI). Two-sided tests were applied. A P value of <.05 was considered statistically significant. Only variables indicating significant associations with RSV or any markers of severe outcomes of RSV in univariable logistic regression models were kept in multivariable logistic regression models, respectively.

We used Stata (version 15) and Microsoft Excel 2010 for the data analyses.

2 | RESULTS

2.1 | Study population (SARI cases)

A total of 413 552 SARI cases were identified from week 01/2009 to 20/2018. More than half (232 340, 56%) of them were male, and 64% (263 133) were ≥65 years old (Figures 1 and 2; Table 2). Of the SARI cases, 46% (188 948) received ARI (J09-J22) as primary discharge diagnosis.

2.2 | RSV cases

A total of 8761 (2%) RSV cases were identified. More than half (4955, 57%) of them were male. Most RSV cases were children aged <5 years (8521, 97%). The mean and median length of hospital stay were 6 and 5 days, respectively. Most (8599, 98%) RSV cases were discharged home, 2% (136) transferred to other facilities, and 0.3% (25) died in hospital. Of the RSV cases, 8228 (94%) received RSV-specific ICD-10 codes as primary discharge diagnosis (J12.1: 2995, 36%; J20.5: 2089, 25%; J21.0: 3144, 38%). Of the total RSV cases, 6773 were from the original sentinel hospitals after 2013 or from the additional sentinel hospitals after 2015 (Figures 1 and 2; Tables 2 and 3).

2.3 | ICU-admitted RSV cases

Of the total RSV cases, 492 (7%) ICU-admitted RSV cases were identified. More than half (262, 53%) of them were male, and 89% (438) were aged <5 years. The mean and median length of ICU stay were 9 and 5 days, respectively. During the ICU stay, 38% (185) required ventilator support. Most (449, 91%) ICU-admitted RSV cases were discharged home, 6% (28) transferred to other facilities, and 3% (15) died in hospital (Figure 2; Table 3).

2.4 | Ventilated RSV cases

Of the 185 ventilated RSV cases, more than half (101, 55%) were male, and 81% (149) were aged <5 years. The mean and median ventilation length were 211 and 112 hours, respectively. Most (152, 82%) ventilated RSV cases were discharged home, 10% (18) transferred to other facilities, and 8% (15) died in hospital (Figure 2; Table 3).

2.5 | Deceased RSV cases

Of the 25 deceased RSV cases, more than half (16, 64%) were female, and nearly half (12, 48%) were ≥65 years old (Table 3). The mean and median length of hospital stay were 27 and 10 days, respectively.

TABLE 1 ICD-10 codes of underlying medical conditions (adapted from Elixhauser and Fleming Comorbidity Indices)

Medical condition	ICD-10 code
Disorder of newborn related to slow fetal growth and fetal malnutrition	P05.-
Extremely low birth weight (<1000 g)	P07.0-
Low birth weight (1000-2499 g)	P07.1-
Extreme immaturity of newborn (<28 weeks)	P07.2
Preterm newborn (28-37 weeks)	P07.3
Respiratory and cardiovascular disorder specific to the perinatal period	P20-P29
Congenital malformation of the heart	Q20-Q24
Congenital malformation of the great vessels	Q25-Q26
Congenital defect originating in perinatal period	Q02, Q30.-, Q32-Q37, Q44.-, Q60.-, Q61.-, P70.0, P70.1, P70.2, P78.8
Down syndrome	Q90.-
Sickle-cell disorder	D57.-
Cystic fibrosis	E84.-
Vitamin D deficiency	E55.-
Asthma	J45.-, J46
Chronic obstructive pulmonary disease (COPD)	J44.-
Chronic pulmonary disease (excl. asthma and COPD)	I27.8, I27.9, J40-J43, J47, J60-J67, J68.4, J70.1, J70.3
Diabetes	E10-E14
Cardiovascular disease	A52.0, I05-I08, I09.1, I09.8, I09.9, I10, I11, I13, I15, I25.5, I26, I27, I28.0, I28.8, I28.9, I34-I39, I42.0, I42.5, I42.9, I43, I44.1-I44.3, I45.6, I45.9, I47-I50, P29.0, Q23.0-Q23.3, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0, Z95.2, Z95.4
Neurological disorders	G10-G13, G20, G22, G25.4, G25.5, G31.2, G31.8, G31.9, G32, G35-G37, G40, G41, G93.1, G93.4, R47.0, R56
Blood disease	D50.0, D50.8, D50.9, D51-D53, D65-D68, D69.1, D69.3-D69.6
Renal failure	I12.0, I13.1, N18, N19, N25, Z49.0, Z49.2, Z94.0, Z99.2
Liver disease	B18, I85, I86, I98, K70, K71.1, K71.3, K71.5, K71.7, K72, K74, K76.0, K76.2, K76.9, Z94.4
Tuberculosis	A15-A19
Cancer	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C85, C88, C96, C90.0, C90.2, C97
HIV/AIDS	B20-B22, B24
Pregnancy	O00-O99

2.6 | RSV cases by calendar week

An overview of the number of total RSV cases and RSV cases with severe outcomes by calendar week is shown from week 01/2015 to 20/2018. During the study period, the most severe season was 2016/17 (Figure 3).

2.7 | RSV cases with underlying medical conditions

The proportion of total RSV cases with different underlying medical conditions varied from 0% to 3.5%. Respiratory and cardiovascular disorder specific to the perinatal period (282, 3.5%) and cardiovascular disease (222, 2.5%) were the most common underlying medical conditions. They both were also the most common underlying medical conditions in the ICU-admitted (60, 12.7%; 69, 14.0%) and ventilated RSV cases (35, 19.0%; 47, 25.4%). Cardiovascular disease (15, 60.0%) and blood disease (9, 36.0%) were the most common underlying medical conditions in deceased RSV cases. RSV cases with underlying sickle-cell disorder (2), tuberculosis (2), and pregnant RSV cases (1; 28 years of age) were rare. No RSV case was diagnosed with HIV/AIDS (Table 4).

2.8 | Univariable analyses of risk factors for RSV and its severe outcomes

In the age-group <5 years, the age-groups 0-5 months and 6 months-1 year (reference group: 2-4 years); being female; the seasons 2012/13, 2014/15, 2016/17, and 2017/18 (reference season: 2013/14); and underlying low birth weight, preterm newborn, and respiratory and cardiovascular disorder specific to the perinatal period were significantly associated with an increased risk of being diagnosed with RSV among SARI cases. Underlying congenital malformation of the heart and great vessels, congenital defect originating in perinatal period, cystic fibrosis, asthma, neurological disorders, blood disease, and cancer were significantly associated with a lower risk of being diagnosed with RSV. Age-group 0-5 months was significantly associated with ICU admission, whereas age-group 2-4 years was significantly associated with death among RSV cases. Gender and season were not associated with any severe outcomes of RSV. Most underlying medical conditions were significantly associated with severe outcomes of RSV.

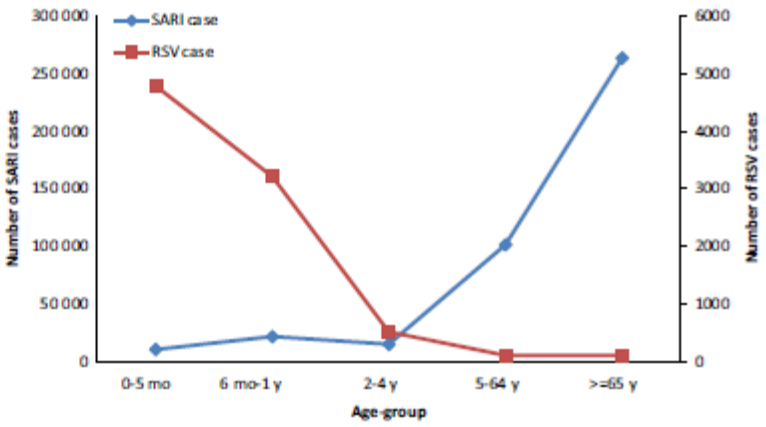

FIGURE 1 Number of SARI cases and RSV cases by age-group, week 01/2009-20/2018

In the age-group ≥5 years, the age-group 5-64 years; the seasons 2012/13, 2014/15, 2016/17, and 2017/18; and underlying congenital defect originating in perinatal period, cystic fibrosis, vitamin D deficiency, asthma, and chronic pulmonary disease were significantly associated with an increased risk of being diagnosed with RSV among SARI cases. Underlying COPD, cardiovascular disease, and renal failure were significantly associated with a lower risk of being diagnosed with RSV. The age-group ≥65 years was associated with death among RSV cases. Gender and season were not associated with any severe outcomes of RSV. Some medical conditions were significantly associated with severe outcomes of RSV.

2.9 | Multivariable analyses of risk factors for RSV in age-group <5 years

Among SARI cases aged <5 years, the age-groups 0-5 months (OR: 20.29, 95% CI: 18.37-22.41) and 6 months-1 year (OR: 4.59, 95% CI: 4.16-5.06); being female (male: OR: 0.85, 95% CI: 0.80-0.89); the seasons 2012/13 (OR: 1.26, 95% CI: 1.12-1.41), 2014/15 (OR: 1.58, 95% CI: 1.42-1.74), 2015/16 (OR: 1.14, 95% CI: 1.03-1.26), 2016/17 (OR: 2.06, 95% CI: 1.88-2.27), and 2017/18 (OR: 1.78, 95% CI: 1.61-1.97); and underlying respiratory and cardiovascular disorder specific to the perinatal period (OR: 1.32, 95% CI: 1.11-1.57) were significantly associated with an increased risk of being diagnosed

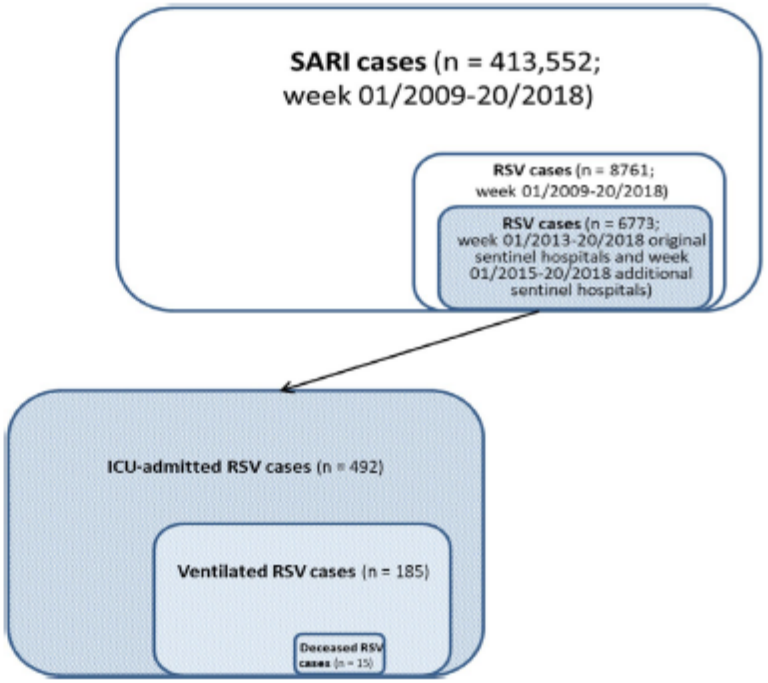

FIGURE 2 Number of SARI cases, RSV cases, ICU-admitted RSV cases, ventilated RSV cases, and deceased RSV cases ever required ventilator support in ICU

TABLE 2 Number of SARI and RSV cases and proportion of RSV cases in SARI cases by age-group, week 01/2009-20/2018

	SARI case	RSV case
Age-group	n	n (%)
0-5 months	11 014	4783 (43)
6 months-1 year	22 207	3213 (14)
2-4 years	15 530	525 (3)
5-64 years	101 668	118 (0.1)
≥65 years	263 133	122 (0.05)
Total	413 552	8761 (2)

with RSV. Underlying congenital malformation of the heart (OR: 0.69, 95% CI: 0.56-0.85) and great vessels (OR: 0.38, 95% CI: 0.26-0.58), congenital defect originating in perinatal period (OR: 0.41, 95% CI: 0.31-0.55), asthma (OR: 0.40, 95% CI: 0.30-0.53), neurological disorders (OR: 0.52, 95% CI: 0.43-0.62), and blood disease (OR: 0.60, 95% CI: 0.48-0.75) were significantly associated with a lower risk of being diagnosed with RSV (Table 5).

2.9.1 | Multivariable analyses of risk factors for severe outcomes of RSV in age-group <5 years

Among RSV cases aged <5 years, the age-group 0-5 months (OR: 2.39, 95% CI: 1.45-3.94), underlying low birth weight (OR: 6.77. 95% CI: 1.28-35.71), preterm newborn (OR: 6.71, 95% CI: 2.19-20.61), respiratory and cardiovascular disorder specific to the perinatal period (OR: 4.97, 95% CI: 3.36-7.34), congenital malformation of the heart (OR: 3.65, 95% CI: 1.90-7.02) and great vessels (OR: 3.50, 95% CI: 1.10-11.18), congenital defect origination in perinatal period (OR: 4.07, 95% CI: 1.71-9.70), cardiovascular disease (OR: 5.19, 95% CI: 2.77-9.72), neurological disorders (OR: 6.48, 95% CI: 3.76-11.18), blood disease (OR: 3.67, 95% CI: 1.98-6.79), and liver disease (OR: 14.99, 95% CI: 1.49-150.82) were significantly associated with ICU admission (Table 5).

Underlying low birth weight (OR: 6.44, 95% CI: 1.56-26.55), preterm newborn (OR: 3.91, 95% CI: 1.20-12.81), respiratory and cardiovascular disorder specific to the perinatal period (OR: 8.82, 95% CI: 5.23-14.89), congenital malformation of the heart (OR: 3.85, 95% CI: 1.63-9.13), congenital defect originating in perinatal period

TABLE 3 RSV cases and RSV cases with severe outcomes by gender and age-group (RSV cases and deceased RSV cases: week 01/2009-20/2018; ICU-admitted RSV cases and ventilated RSV cases: week 01/2013-20/2018 original sentinel hospitals, week 01/2015-20/2018 additional sentinel hospitals)

	RSV cases		ICU-admitted RSV cases		Ventilated RSV cases		Deceased RSV cases	
	Male	Female	Male	Female	Male	Female	Male	Female
Age-group	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
0-5 months	2684 (54)	2099 (55)	164 (63)	164 (71)	61 (60)	53 (63)	0 (0)	3 (19)
6 months-1 year	1875 (38)	1338 (35)	54 (21)	35 (15)	17 (17)	10 (12)	2 (22)	3 (19)
2-4 years	273 (6)	252 (7)	12 (5)	9 (4)	3 (3)	5 (6)	1 (11)	1 (6)
5-64 years	62 (1)	56 (1)	13 (5)	5 (2)	6 (6)	2 (2)	1 (11)	2 (13)
≥65 years	61 (1)	61 (2)	19 (7)	17 (7)	14 (14)	14 (17)	5 (56)	7 (44)
Total	4955	3806	262	230	101	84	9	16

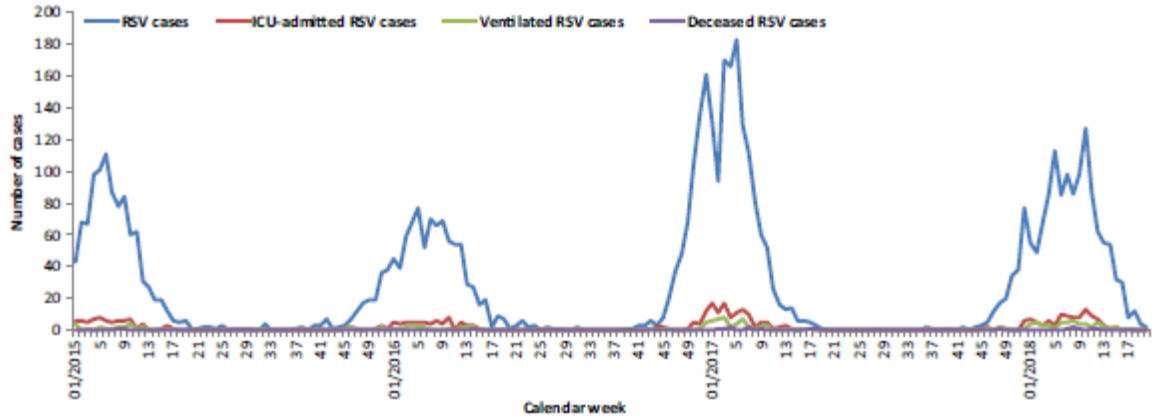

FIGURE 3 Number of RSV cases and RSV cases with severe outcomes by calendar week, week 01/2015-20/2018

TABLE 4 RSV cases and RSV cases with severe outcomes by underlying medical condition (RSV cases and deceased RSV cases: week 01/2009-20/2018; ICU-admitted RSV cases and ventilated RSV cases: week 01/2013-20/2018 original sentinel hospitals, week 01/2015-20/2018 additional sentinel hospitals)

	N (%) of RSV cases n = 8761	N (%) of ICU-admitted RSV cases n = 492	N (%) of ventilated RSV cases n = 185	N (%) of deceased RSV cases n = 25
Medical condition				
Disorder of newborn related to slow fetal growth and fetal malnutrition	6 (0.1)	1 (0.2)	0	0
Extremely low birth weight (<1000 g)	9 (0.1)	3 (0.6)	3 (1.6)	0
Low birth weight (1000-2499 g)	51 (0.6)	16 (3.4)	12 (6.5)	0
Extreme immaturity of newborn (<28 weeks)	8 (0.1)	3 (0.6)	3 (1.6)	0
Preterm newborn (28-37 weeks)	62 (0.8)	21 (4.4)	14 (7.6)	0
Respiratory and cardiovascular disorder specific to the perinatal period	282 (3.5)	60 (12.7)	35 (19.0)	1 (4.0)
Congenital malformation of the heart	131 (1.6)	35 (7.4)	19 (10.3)	2 (8.0)
Congenital malformation of the great vessels	34 (0.4)	13 (2.8)	8 (4.4)	0
Congenital defect originating in perinatal period	61 (0.7)	14 (2.9)	8 (4.3)	1 (4.0)
Down syndrome	42 (0.5)	9 (1.9)	2 (1.1)	0
Sickle-cell disorder	2 (0.0)	0	0	0
Cystic fibrosis	9 (0.1)	1 (0.2)	1 (0.5)	0
Vitamin D deficiency	13 (0.2)	3 (0.6)	3 (1.6)	1 (4.0)
Asthma	63 (0.7)	4 (0.8)	1 (0.5)	0
Chronic obstructive pulmonary disease (COPD)	43 (0.5)	11 (2.2)	8 (4.3)	3 (12.0)
Chronic pulmonary disease (excl. asthma and COPD)	54 (0.6)	5 (1.0)	5 (2.7)	2 (8.0)
Diabetes	62 (0.7)	16 (3.3)	12 (6.5)	4 (16.0)
Cardiovascular disease	222 (2.5)	69 (14.0)	47 (25.4)	15 (60.0)
Neurological disorders	167 (1.9)	34 (6.9)	18 (9.7)	8 (32.0)
Blood disease	129 (1.5)	33 (6.7)	25 (13.5)	9 (36.0)
Renal failure	65 (0.7)	22 (4.5)	14 (7.6)	6 (24.0)
Liver disease	24 (0.3)	8 (1.6)	5 (2.7)	5 (20.0)
Tuberculosis	2 (0.0)	1 (0.2)	1 (0.5)	0
Cancer	27 (0.3)	4 (0.8)	2 (1.1)	1 (4.0)
HIV/AIDS	0	0	0	0
Pregnancy	1 (0.0)	0	0	0

(OR: 3.30, 95% CI: 1.05-10.34), cystic fibrosis (OR: 35.13, 95% CI: 1.76-700.59), cardiovascular disease (OR: 5.96, 95% CI: 2.71-13.08), neurological disorders (OR: 4.43, 95% CI: 2.05-9.56), blood disease (OR: 8.22, 95% CI: 4.13-16.36), and liver disease (OR: 13.70, 95% CI: 1.81-103.80) were significantly associated with application of ventilator support (Table 5).

Underlying chronic pulmonary disease (OR: 12.58, 95% CI: 1.13-140.15), cardiovascular disease (OR: 9.42, 95% CI: 1.46-60.82), neurological disorders (OR: 21.70, 95% CI: 4.98-94.51), blood disease (OR: 12.17, 95% CI: 2.23-66.26), and liver disease (OR: 170.86, 95% CI: 20.54-1421.11) were significantly associated with an increased risk of death (Table 5).

2.10 | Multivariable analyses of risk factors for RSV in age-group ≥5 years

Among SARI cases aged ≥5 years, the age-group 5-64 years (≥65 years: OR: 0.53, 95% CI: 0.39-0.71); the seasons 2012/13 (OR: 2.74, 95% CI: 1.38-5.45), 2014/15 (OR: 2.15, 95% CI: 1.12-4.15),

TABLE 5 Multivariable logistic regression analyses of risk factors for RSV and its severe outcomes in age-group <5 years (RSV cases and deceased RSV cases: week 01/2009-20/2018; ICU-admitted RSV cases and ventilated RSV cases: week 01/2013-20/2018 original sentinel hospitals, week 01/2015-20/2018 additional sentinel hospitals)

	RSV case		ICU-admitted RSV case		Ventilated RSV case		Deceased RSV case	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age-group								
0-5 months	20.29	18.37-22.41	2.39	1.45-3.94			0.28	0.03-2.29
6 months-1 year	4.59	4.16-5.06	0.87	0.52-1.48			0.63	0.10-4.21
2-4 years (reference group)	1		1				1	
Gender								
Male	0.85	0.80-0.89						
Female (reference group)	1							
Season								
2009/10	0.38	0.31-0.45						
2010/11	0.93	0.82-1.07						
2011/12	0.90	0.79-1.02						
2012/13	1.26	1.12-1.41						
2013/14 (reference group)	1							
2014/15	1.58	1.42-1.74						
2015/16	1.14	1.03-1.26						
2016/17	2.06	1.88-2.27						
2017/18	1.78	1.61-1.97						
Medical condition								
Low birth weight (1000-2499 g)	1.18	0.72-1.93	6.77	1.28-35.71	6.44	1.56-26.55		
Preterm newborn (28-37 weeks)	1.43	0.92-2.24	6.71	2.19-20.61	3.91	1.20-12.81		
Respiratory and cardiovascular disorder specific to the perinatal period	1.32	1.11-1.57	4.97	3.36-7.34	8.82	5.23-14.89		
Congenital malformation of the heart	0.69	0.56-0.85	3.65	1.90-7.02	3.85	1.63-913	2.54	0.26-24.78
Congenital malformation of the great vessels	0.38	0.26-0.58	3.50	1.10-11.18	1.87	0.46-7.68		
Congenital defect originating in perinatal period	0.41	0.31-0.55	4.07	1.71-9.70	3.30	1.05-10.34	2.61	0.23-29.68
Down syndrome			2.61	0.93-7.31				

(Continues)

TABLE 5 (Continued)

	RSV case		ICU-admitted RSV case		Ventilated RSV case		Deceased RSV case	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Cystic fibrosis	0.26	0.06-1.13			35.13	1.76-700.59		
Vitamin D deficiency					9.02	0.88-92.32		
Asthma	0.40	0.30-0.53						
Chronic pulmonary disease (excl. asthma and COPD)					3.67	0.69-19.46	12.58	1.13-140.15
Cardiovascular disease			5.19	2.77-9.72	5.96	2.71-13.08	9.42	1.46-60.82
Neurological disorders	0.52	0.43-0.62	6.48	3.76-11.18	4.43	2.05-9.56	21.70	4.98-94.51
Blood disease	0.60	0.48-0.75	3.67	1.98-6.79	8.22	4.13-16.36	12.17	2.23-66.26
Liver disease			14.99	1.49-150.82	13.70	1.81-103.80	170.86	20.54-1421.11
Cancer	0.60	0.17-2.07						

Note: Statistically significant results appear in bold.

2016/17 (OR: 4.41, 95% CI: 2.43-7.99), and 2017/18 (OR: 8.51, 95% CI: 4.78-15.15); and underlying congenital defect originating in perinatal period (OR: 3.74, 95% CI: 1.19-11.76), cystic fibrosis (OR: 13.40, 95% CI: 5.83-30.78), vitamin D deficiency (OR: 2.57, 95% CI: 1.12-5.93), and chronic pulmonary disease (OR: 2.04, 95% CI: 1.23-3.38) were significantly associated with an increased risk of being diagnosed with RSV (Table 6).

2.11 | Multivariable analyses of risk factors for severe outcomes of RSV in age-group ≥5 years

Among RSV cases aged ≥5 years, underlying blood disease was significantly associated with ICU admission (OR: 4.38, 95% CI: 1.56-12.27), application of ventilator support (OR: 3.40, 95% CI: 1.22-9.55), and death (OR: 7.17, 95% CI: 1.31-19.15). Underlying renal failure (OR: 2.27, 95% CI: 1.13-4.55) was significantly associated with ICU admission. The age-group ≥65 years (OR: 5.01, 95% CI: 1.31-19.15) was significantly associated with an increased risk of death (Table 6).

3 | DISCUSSION

The ICOSARI surveillance data enabled us to describe epidemiology of hospitalized RSV in Germany and to identify risk factors for being diagnosed with RSV and severe outcomes of RSV in hospital. Besides the previously known risk factors for RSV and its severe outcomes including young age, certain underlying neonatal disorders, and chronic pulmonary and cardiovascular diseases, underlying cystic fibrosis and vitamin D deficiency were also found to be risk factors for being diagnosed with RSV. For severe outcomes of RSV, age-group ≥65 years, underlying cystic fibrosis, neurological disorders, blood disease, liver disease, and renal failure were found to be risk factors.

In our study, the majority of SARI cases were older adults, whereas most RSV cases were young children. However, almost half of the deceased RSV cases were older adults. The ICU admission rate among hospitalized RSV cases (2%-19%) and RSV fatality rate (0%-5%) vary in different studies.[1,12,19-21] Our results are within these ranges. In our study, the deceased RSV cases stayed in hospital in average longer than other RSV cases. RSV fatality rate was at least 10 times higher among ICU-admitted and ventilated RSV cases than other RSV cases. The number of RSV cases was higher in the season 2016/17 during the study period which is in line with the finding of the RSV surveillance in the United States.[22] The majority of RSV cases were without the underlying medical conditions in our study. However, in most deceased RSV cases, underlying cardiovascular disease was present.

The majority of RSV cases were aged <5 years in our study. Thus, we investigated risk factors separately in two age-groups <5 and ≥5 years. To avoid confounding effects, we included in the multivariable models variables with significant association with RSV or its severe outcomes in the univariable models.

In the multivariable models for the age-group <5 years, among SARI cases, children in the first months of life were significantly more likely to be diagnosed with RSV, and among RSV cases, they were more likely to be admitted to ICU. Our findings are concordant with the majority of reports that young age is a risk factor for hospitalization due to RSV[1,2,10] and age below 3 months contributes to the increased severity of RSV disease.[25] Being male is normally known to be a risk factor for RSV.[10,24] However, Grimwood et al reported non-significant association between being male and RSV.[25] In our study, being female was a risk factor for being diagnosed with RSV, and gender did not play a role in developing severe outcomes of RSV. The association between RSV and season varied across the 9 seasons. RSV was more likely to be diagnosed in the seasons 2016/17 and 2017/18.

Low birth weight and prematurity are widely recognized as important risk factors for RSV.[8–10] In our study, they were not associated with being diagnosed with RSV, but were risk factors for ICU admission and application of ventilator support in RSV cases. Immature immune system, poorly developed airway, and reduced respiratory muscle capacity of premature infants may contribute to this risk.[9,26] Children with underlying congenital heart and great vessel disease, congenital defect originating in perinatal period, neurological disorders, and blood disease were significantly more likely to be diagnosed with other SARI compared to RSV in our study. However, the above-mentioned underlying medical conditions, underlying cystic fibrosis, chronic pulmonary disease, cardiovascular disease, and liver disease still contributed to the severe outcomes among RSV cases. Our findings are in agreement

TABLE 6 Multivariable logistic regression analyses of risk factors for RSV and its severe outcomes in age-group ≥5 years (RSV cases and deceased RSV cases: week 01/2009-20/2018; ICU-admitted RSV cases and ventilated RSV cases: week 01/2013-20/2018 original sentinel hospitals, week 01/2015-20/2018 additional sentinel hospitals)

	RSV case		ICU-admitted RSV case		Ventilated RSV case		Deceased RSV case	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age-group								
5-64 years (reference group)	1						1	
≥65 years	**0.53**	**0.39-0.71**					**5.01**	**1.31-19.15**
Season								
2009/10	0.60	0.17-2.11						
2010/11	1.29	0.52-3.21						
2011/12	1.65	0.73-3.73						
2012/13	**2.74**	**1.38-5.45**						
2013/14 (reference group)	1							
2014/15	**2.15**	**1.12-4.15**						
2015/16	1.71	0.87-3.39						
2016/17	**4.41**	**2.43-7.99**						
2017/18	**8.51**	**4.78-15.15**						
Medical condition								
Congenital defect originating in perinatal period	**3.74**	**1.19-11.76**						
Cystic fibrosis	**13.40**	**5.83-30.78**						
Vitamin D deficiency	**2.57**	**1.12-5.93**						
Asthma	1.73	0.96-3.12						
Chronic obstructive pulmonary disease (COPD)	0.75	0.50-1.11						
Chronic pulmonary disease (excl. asthma and COPD)	**2.04**	**1.23-3.38**						
Cardiovascular disease	0.71	0.53-0.96						
Blood disease			**4.38**	**1.56-12.27**	**3.40**	**1.22-9.50**	**7.17**	**1.31-19.15**
Renal failure	0.77	0.56-1.06	**2.27**	**1.13-4.55**				

Note: Statistically significant results appear in bold.

with the reports that among infants, underlying congenital heart disease or lung disease increases severity of hospitalized RSV,[27-29] and RSV infection is more severe in those with underlying cystic fibrosis.[9,50,51] Poor growth and malnutrition are symptoms of cystic fibrosis which may affect pulmonary function and have an impact on the severity of RSV disease in infants with RSV and cystic fibrosis.[9,51]

In the multivariable models for the age-group ≥5 years, older adults were significantly unlikely to be diagnosed with RSV. However, they were significantly more likely to have severe outcome of death if they were diagnosed with RSV. This finding can be explained that RSV similar to seasonal influenza can cause severe respiratory complications in older adults, resulting in respiratory failure and high mortality.[52] Gender was not associated with RSV or its severe outcomes. Like the age-group <5 years, RSV was more likely to be diagnosed in the seasons 2016/17 and 2017/18. Although underlying cystic fibrosis normally increases severity of RSV in infants,[9,50,51] in our study, it was also a risk factor for being diagnosed with RSV in older children and adults. Our results regarding vitamin D deficiency are in line with the findings that vitamin D may protect against RSV-associated ALRI since vitamin D may influence the development of immune system, modulate early lung development, and decrease viral load during infection,[53] but vitamin D deficiency is not associated with the increased severity of RSV.[54]

Underlying Down syndrome was reported as a risk factor for RSV in some studies,[10,55] whereas some other studies did not find the association.[10,20] In our study, it was like underlying disorder of newborn related to slow fetal growth and fetal malnutrition, diabetes, and cancer not associated with RSV or its severe outcomes in both age-groups. The young age is associated with hospitalized RSV.[1,2,10] However, children with Down syndrome that are admitted to the hospital tend to be older than children with RSV infection.[55] This may partly explain our finding regarding the Down syndrome. RSV and other respiratory pathogens in early life play an important role in the inception and exacerbation of asthma.[56,57] We investigated underlying asthma as a possible risk factor for RSV and its severe outcomes. In age-group <5 years, asthma patients were more likely to be diagnosed with other SARI compared to RSV, and in age-group ≥5 years, no associations were found. However, RSV may be underdiagnosed in asthma patients due to similar clinical presentation, if no fever is present. COPD patients may be more susceptible to RSV infection[58]; however, we found no associations. In our study, the number of RSV cases with underlying sickle-cell disorder, tuberculosis, and pregnant RSV cases was too low to support the data analyses. Underlying neurological disorders, blood disease, liver disease, and renal failure have been rarely investigated as possible risk factors for RSV or its severe outcomes in the literature. In our study, they contributed to the severe outcomes in RSV cases.

Our study has some limitations. Based on the hospitalization data alone, information on socio-demographic factors except age and gender as well as environmental factors for RSV could not be captured. Thus, socio-demographic and environmental factors and underlying medical conditions could not be evaluated in one model, which limited a comprehensive understanding of the risk factors for RSV and its severe outcomes. Further, no data were available to identify any children who had received palivizumab which would reduce the strength of association with risk factors. ICOSARI is a ICD-10-based syndromic surveillance system. Virological data of the ICOSARI network were not available. As the coding behavior of physicians may vary based on use of laboratory diagnostics and level of coding awareness, some true cases may be missed or wrongly included due to miscoding which could lead to information bias. RSV is also a common pathogen of ARI in older adults. In our study, among those aged ≥65 years, the proportion of RSV cases in SARI cases was lower than that reported in the literature.[59] Our data suggest that in elderly SARI patients, RSV testing might be less frequently carried out. Thus, in our analysis we always use the expression being diagnosed with RSV not RSV infection. Also for this reason, we realized that we cannot exclude underdiagnosis of RSV, leading to underestimation of risks. Although the sample size of our study population and RSV cases was large, the number of deceased RSV cases and RSV cases with some underlying medical conditions was small which may lead to sparse data bias, especially for the evaluation of risk factors for deceased RSV cases and underlying liver disease as risk factor in age-group <5 years. However, few other studies were large enough to look into the risk of death, whereas our approach using surveillance data, despite this limitation, allowed analysis of deceased RSV cases.

4 | CONCLUSIONS

Using ICD-10-based surveillance data allows to identify risk factors for being diagnosed with RSV and severe outcomes of RSV in hospital, to quantify the risk in different age-groups, and to monitor the risk routinely. Our findings will contribute to the development of a baseline for evaluating RSV vaccination strategies and RSV vaccination impact in the future, in particular on the target groups, and help reducing burden of RSV disease and its severe outcomes.

Further studies regarding risk factors for RSV are needed with the focus on the underlying medical conditions with inconsistent findings compared with the literature with consideration of socio-demographic and environmental factors.

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CONFLICT OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Wei Cai, Silke Buda, Walter Haas, Siddhivinayak Hirve, and Wenqing Zhang were involved in designing the study. Silke Buda and Ekkehard

Schuler participated in the collection of ICOSARI data. Wei Cai analyzed the data and drafted the manuscript. All authors reviewed and approved the final manuscript.

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Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

List of publications

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