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Intensive care unit surveillance of influenza infection in France: the 2009/10 pandemic and the three subsequent seasons

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During the 2009/10 pandemic, a national surveillance system for severe influenza cases was set up in France. We present results from the system's first four years. All severe influenza cases admitted to intensive care units (ICU) were reported to the Institut de Veille Sanitaire using a standardised form: data on demographics, immunisation and virological status, risk factors, severity (e.g. acute respiratory distress syndrome (ARDS) onset, mechanical ventilation, extracorporeal life support) and outcome. Multivariate analysis was performed to identify factors associated with ARDS and death. The number of confirmed influenza cases varied from 1,210 in 2009/10 to 321 in 2011/12. Most ICU patients were infected with A(H1N1) pdm09, except during the 2011/12 winter season when A(H3N2)-related infections predominated. Patients' characteristics varied according to the predominant strain. Based on multivariate analysis, risk factors associated with death were age ≥ 65 years, patients with any of the usual recommended indications for vaccination and clinical severity. ARDS occurred more frequently in patients who were middle-aged (36–55 years), pregnant, obese, or infected with A(H1N1) pdm09. Female sex and influenza vaccination were protective. These data confirm the persistent virulence of A(H1N1)pdm09 after the pandemic and the heterogeneity of influenza seasons, and reinforce the need for surveillance of severe influenza cases.

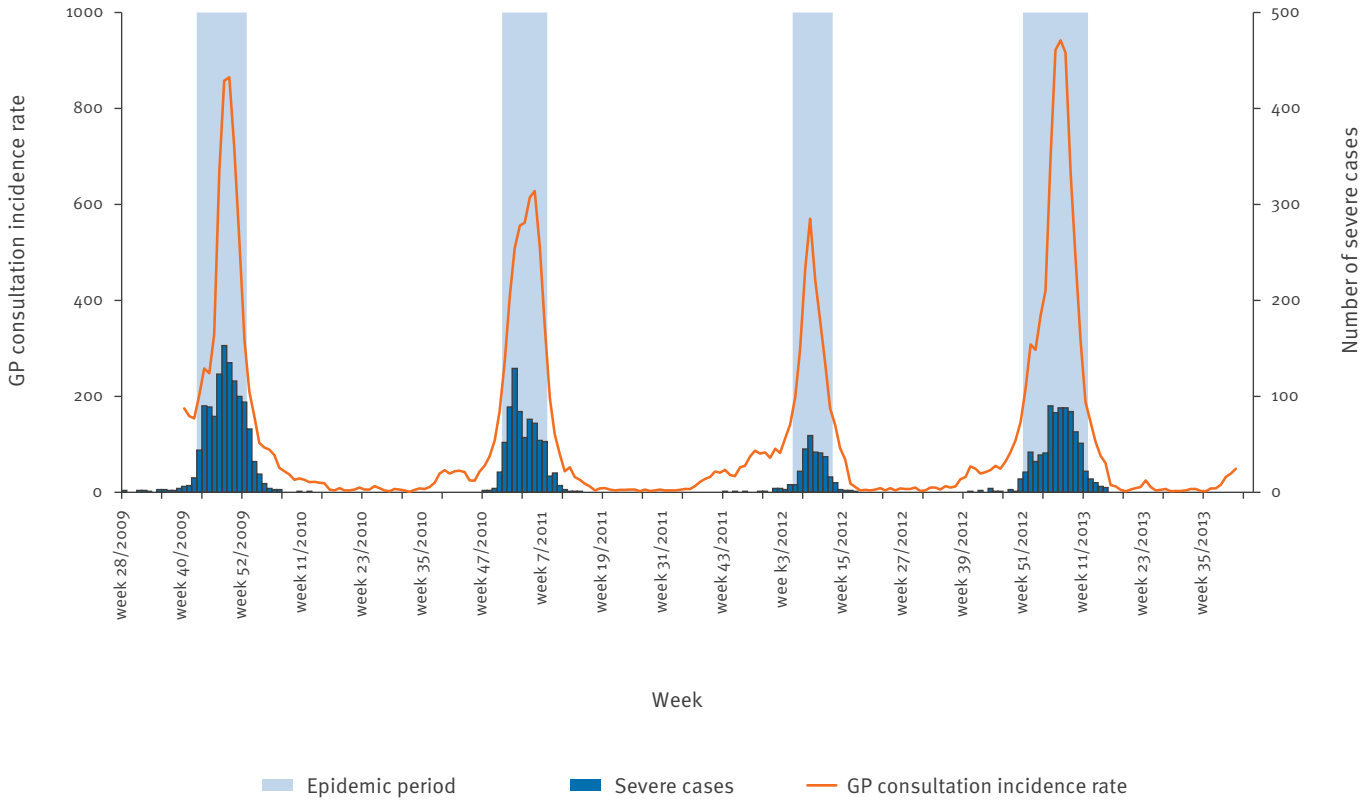
Introduction

Historically, the epidemiological surveillance of influenza in France has mainly been carried out in general practice, through two networks: the Réseau des Grog [1] and Sentinelles [2]. The Réseau des Grog also collected nasopharyngeal specimens for virological surveillance. During the 2009/10 pandemic, those two networks uploaded their data to the same database and for the first time, used a common case definition (sudden onset of fever (> 39 °C) with myalgia and respiratory signs). An intensive care unit (ICU) surveillance system was created to monitor severe cases of influenza [3]. Clinicians were asked to report all influenza cases admitted to ICUs to the French Institute for Public Health Surveillance (Institut de veille sanitaire-InVS). Both biologically confirmed and probable (based on clinician clinical judgement) influenza cases had to be notified. Biological confirmation relied on a positive influenza reverse transcriptase-PCR (RT-PCR) performed on a respiratory sample. This ICU surveillance was maintained after the pandemic season. Data collected were restricted to a one-page standardised notification form which was forwarded to the InVS regional offices (Cire). In order to reach a high level of notification, each of the 17 Cires regularly contact the ICUs in their own region to ensure that all influenza cases are reported, to complete the missing information and to follow patients' evolution until ICU discharge or death. They also regularly matched the ICUs surveillance data with the hospital virological database. The adult and paediatric French Societies of Anaesthesia and Critical Care Medicine provided strong support for this surveillance.

The surveillance system was exhaustive except in December 2010: the surveillance started with an ICU sentinel network in week 50 in 2010 and was extended to all ICUs in week 01 in 2011 due to the worryingly high number of influenza-based ICU admissions reported in the United Kingdom [4].

Figure 1

Weekly number of severe influenza admissions to intensive care and weekly general physician consultation incidence rate, France, week 28/2009 to week 17/2012



A(H1N1)-associated ICU admissions data during the pandemic and the following season have been described extensively [3,5-7]. However, little has been published on the characteristics of severe influenza cases hospitalised in ICU during seasonal influenza. We used the first four years of ICU surveillance to describe and compare patient characteristics according to the season and the influenza virus circulating, and we looked at the risk factors associated with death and acute respiratory distress syndrome (ARDS).

Methods

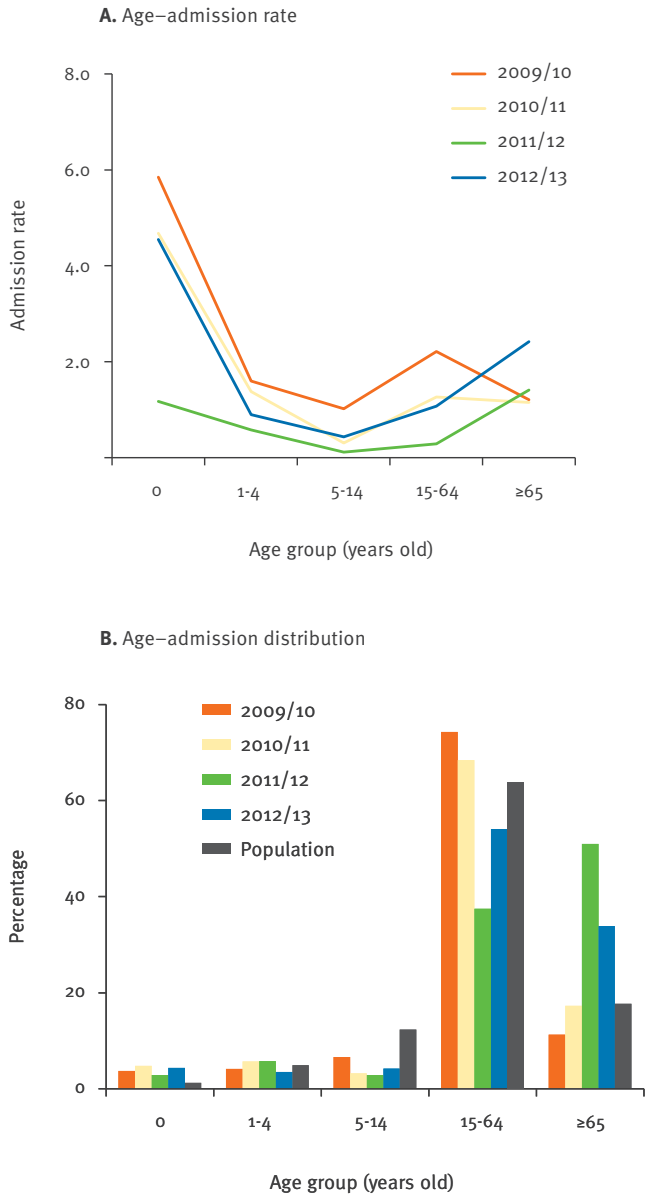
This study included only laboratory-confirmed influenza cases admitted to ICU in mainland France that were reported during the pandemic (2009/10) and the subsequent three winter seasons. The data collected were as follows: demographics (age, sex, region); date of ICU admission; up to three non-exclusive risk factors for severe influenza as follows: (i) obesity (defined by body mass index (body mass index (BMI) ≥ 30 kg/m^2), (ii) pregnancy and (iii) belonging to the vaccine-targeted group according to recommendations (patients with chronic disease [8] or over 65 years old); influenza vaccination status (except during the pandemic); viral type and subtype; severity (ARDS presentation, need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO)); and outcome (discharge or death). All dichotomous variables were formatted as a yes/no answer, except for ECMO and mechanic ventilation where only affirmative answers were collected.

With the exception of the pandemic year, when surveillance started in July, seasonal influenza surveillance usually ran from mid-November or the beginning of December until April. Surveillance was exhaustive, except in December 2010 when the severe case surveillance started with an ICU sentinel network in most regions. To take into account these three weeks of sentinel surveillance in all regions, the number of cases reported during these three weeks (N_{Sent_o}) in each region was divided by the proportion of cases notified by the ICU sentinel hospitals in this region after surveillance extension (N_{Sent_1} / [$N_{Sent_1} + N_{NonSent_1}$]). For that season, the number of admissions by age was estimated by applying the age distribution of observed cases to the extrapolated number of admissions.

Weekly ICU admission rates were compared with weekly estimated incidence of influenza-like illness (ILI) consultations, obtained from the general practitioners (GP) surveillance network. In the present study, we also compared the virus distribution among ICU patients and GP patients. Average population figures from 2009 to 2012, provided by the Institut national de la statistique et des études économiques (Insee), were used to calculate the French population age distribution. The age-specific admission rates for each season were calculated using yearly population data, starting with 2009 figures for the 2009/10 season.

Figure 2

Age–admission rate (A) and age–admission distribution (B) of severe influenza cases in intensive care units, compared with age-distribution in the general population, France, influenza seasons 2009/10 to 2012/13



Influenza epidemic periods were those defined by Sentinelles: this GP network used an epidemic threshold based on a periodic regression model [9].

The percentage of missing data for different variables and seasons ranged from 1% to 32% (Table 1). In order to reduce potential bias arising from complete-case analysis and because the missing at random (MAR) assumption was plausible for the incomplete variables, we performed multiple imputations by chained equations to deal with missing values (non-subtyped A virus treated as missing data). Stata›s user-written programme ice was used. We created 100 complete datasets. Except for the admission date, all the variables were included in the imputation procedures, as were all the possible interactions.

A descriptive study was first undertaken using multiple imputation analysis. Two multivariate logistic regressions were performed to identify factors associated with death and ARDS. All independent variables, including age, were defined as categorical. Including age as a continuous variable required techniques (fractional polynomials, splines), difficult to use with multiple imputation data. Age groups were defined as follows: 0–35 years, 36–55 years, and›56 years. Obesity or pregnancy with no other risk factor were differentiated from the risk factors defined above. We set up three levels of disease severity: no ARDS (score 0), ARDS not requiring ECMO (score 1) and ARDS requiring ECMO (score 2). With the exception of the date of admission, all variables were considered eligible for the model and were tested using logistic regression. For each non-dichotomous variable with several categories, the reference chosen was the category with the closest proportion to the proportion of death (or ARDS) among ICU cases as a whole. A variable was considered to be associated with death (or ARDS) in the multivariate analysis if the p value was ≤ 0.05. As data on vaccination status were not properly collected in 2009/10, we tested its association with death (or ARDS) in a multivariate analysis for the post-pandemic period. If vaccination was associated with death (or ARDS), we kept the variable, excluding the 2009/10 data. If not, we removed it from the final model and performed an analysis on the whole period, including 2009/10.

The analysis was performed using Stata 12. For the descriptive and multivariate analysis, the results based on multiple imputations were compared with results restricted to complete cases.

Results

Throughout the four seasons, 3,074 confirmed cases were notified, representing 95% of all probable and confirmed notified cases. The epidemic period began in the weeks starting 12 October 2009, 20 December 2010, 30 January 2012 and 17 December 2012 and lasted 10, 9, 8, and 13 weeks respectively. The first severe influenza cases to be reported were admitted 14 weeks before the onset of the pandemic wave, and 4, 14 and 11 weeks before the epidemic threshold was reached during the subsequent seasons. The epidemic curve of the weekly admissions to ICU was almost parallel to the weekly influenza-like illness GP consultation rate curve (Figure 1).

During the surveillance period, the number of reported cases decreased dramatically from 1,210 during the pandemic to 312 in 2011/12. During the epidemic periods, around 90% of the cases were admitted and the same trend was observed with a number of admissions varying from 1,038 during the pandemic to 270 in 2011/12. If the surveillance system had been exhaustive in December 2010, the number of cases would have been 793 during the 2010/11 season.

Table 1

Characteristics of influenza cases admitted to intensive care units by influenza season, France, influenza seasons 2009/10–2012/13

ICU cases	2009/10			2010/11			2011/12			2012/13		
	Missing data	CC	Multiple imputation (95% CI)	Missing data	CC	Multiple imputation (95% CI)	Missing data	CC	Multiple imputation (95% CI)	Missing data	CC	Multiple imputation (95% CI)
Age and sex												
Mean age (years)	0%	40.9	40.9 (39.7–42.1)	1%	44.6	44.6 (42.9–46.2)	0%	58.5	58.5 (55.8–61.3)	0%	52.7	52.7 (51.0–54.3)
Male	0%	53%	53% (50–56)	1%	58%	58% (54–61)	0%	55%	55% (49–60)	0%	54%	54% (51–58)
Risk factors	1%			2%			1%			1%		
None	–	27%	27% (24–29)	–	35%	35% (32–39)	–	18%	18% (14-23)	–	22%	22% (19-25)
Chronic disease and age≥65	–	63%	63% (60–66)	–	50%	50% (46–53)	–	80%	80% (76–85)	–	72%	72% (69–75)
Pregnancy with no other risk factor	–	3%	3% (2–4)	–	4%	4% (3–5)	–	1%	1% (0–2)	–	1%	1% (0–2)
Obesity with no associated risk factor	–	7%	7% (6–9)	–	11%	11% (9–13)	–	1%	1% (0–2)	–	5%	5% (3-6)
Pregnancy [a]	–	5%	5% (4–6)	–	4%	4% (3–5)	–	1%	1% (0–2)	–	2%	2% (0–2)
Obesity>17 years-old [a]	–	20%	20% (17-22)	–	23%	23% (20–26)	–	16%	16% (11-20)	–	15%	15% (12–18)
Seasonal vaccination												
Vaccinated [b]	–	–	–	31%	12% (n=63)	13% (10–16)	25%	28% (n=66)	29% (23–34)	31%	16% (n=89)	16% (13–19)
Influenza severity												
ARDS	0%	46%	46% (43–49)	1%	64%	64% (60–67)	0%	43%	43% (37–48)	0%	50%	50% (46–53)
ECMO	–	7%	7% (6–8)	–	10%	10% (8–12)	NA	3%	3% (1–5)	–	7%	7% (5–8)
Mechanical ventilation	22%	59%	59% (56–62)	–	66%	66% (62–69)	NA	62%	62% (56–67)	–	64%	64% (61–68)
Death [b]	32%	27% (n=221)	18% (16–20)	0%	20% (n=148)	20% (17–23)	1%	16% (n=49)	16% (12–20)	1%	19% (n=152)	19% (16–22)
Severity score												
Score 0: No ARDS	–	54%	54% (51–57)	–	36%	36% (33–40)	–	57%	57% (52–63)	–	51%	50% (47–54)
Score 1: ARDS with no ECMO	–	39%	39% (37–42)	–	54%	54% (51–58)	–	40%	40% (35–46)	–	43%	43% (40–46)
Score 2: ARDS with ECMO	–	7%	7% (6–8)	–	10%	10% (8–12)	–	3%	3% (1–5)	–	7%	6% (5–8)
Laboratory results												
A(H1N1)pdm09	–	94%	100%	–	60%	85% (83–88)	–	6%	15% (9-21)	–	25%	46% (42–51)
A(H3N2)	–	0%	–	–	2%	3% (2–5)	–	39%	83% (77–89)	–	12%	23% (19–27)
Non-subtyped A	–	6%	–	–	27%	–	–	53%	–	–	32%	–
B	–	0%	–	–	11%	11% (9–14)	–	2%	2% (0–3)	–	31%	31% (28–34)
Total observations	–	**1,210**	–	–	**746**	–	–	**312**	–	–	**806**	–
Virus testing at GP practices												
A(H1N1)pdm09	–	95%	–	–	40%	–	–	4%	–	–	21%	–
A(H3N2)	–	0%	–	–	6%	–	–	86%	–	–	18%	–
Non sub-typed A	–	5%	–	–	8%	–	–	5%	–	–	6%	–
B	–	0%	–	–	46%	–	–	5%	–	–	55%	–

ARDS: acute respiratory distress syndrome; CC: complete case; CI: confidence interval; ECMO: extracorporeal membrane oxygenation; GP: general practitioner; ICU: intensive care unit; –: not applicable.

Virus distribution generated through general practitioner-based sentinel surveillance.

[a] With or without associated risk factor

[b] Numerator in bracket

Table 2

Bivariate analysis of death and multivariate analysis to identify risk factors associated with death in influenza patients, France, influenza seasons 2009/10–2012/13

	Univariate analysis		Multivariate analysis					
	Complete cases	Multiple imputation (95% CI)	Complete cases (n = 2,041)			Multiple imputation (n = 3,034)		
			OR	95% CI		OR	95% CI	
Age								
0–35 years	13%	11% (9–13)	0.7	0.5	1.0	0.7	0.5	0.9
36–55 years	22%	18% (16–21)	Ref			Ref		
>55 years	26%	24% (22–26)	1.2	0.9	1.6	1.5	1.2	1.9
Sex								
Male	22%	19% (17–21)	Not included					
Female	21%	18% (19–20)						
Risk factors								
None	14%	12% (10–14)	0.4	0.3	0.6	0.5	0.4	0.6
Chronic disease and age ≥ 65 years	25%	22% (20–24)	Ref			Ref		
Pregnancy with no other risk factor	13%	11% (4–18)	0.3	0.1	0.6	0.3	0.1	0.7
Obesity with no other risk factor	18%	15% (10–20)	0.4	0.2	0.6	0.4	0.3	0.6
Seasonal vaccination (2009/10 excluded)								
No	17%	19% (17–21)	Not included					
Yes	17%	19% (13–24)						
Severity								
Score 0: No ARDS	10%	8% (7–10)	Ref			Ref		
Score 1: ARDS with no ECMO	30%	27% (25–29)	4.0	3.0	5.2	4.2	3.3	5.3
Score 2: ARDS with ECMO	45%	39% (33–46)	10.8	7.1	16.3	10.7	7.4	15.4
Virus								
A(H1N1)	25%	19% (18–21)	Ref			Ref		
A(H3N2)	19%	16% (13–20)	0.7	0.5	1.1	0.8	0.6	1.2
B	17%	16% (12–20)	0.6	0.5	0.9	0.8	0.6	1.2

ARDS; acute respiratory distress syndrome; CI: confidence intervals; ECMO: extracorporeal membrane oxygenation; OR: odds ratio; Ref: reference value.

Significant OR ($p < 0.05$) shown in grey.

Virus A was predominant among ICU cases in the four seasons studied, the proportion varying from 100% during the pandemic to 69% in 2012/13. When compared with the distribution among influenza-confirmed GP patients, the virus A(H1N1)pdm09 was always over-represented among ICU cases, for instance, representing 40% of the influenza-confirmed GP patients and 85% of the influenza-confirmed ICU patients in 2010/11 (Table 1).

ICU admission rate by age group described a U-shaped curve in 2011/12 and 2012/13 but not in 2009/10 and 2010/11. These two latter seasons were characterised by a large A(H1N1)pdm09 circulation and admission rates among the 15–64 year-old patients were equal or superior to the admission rate for those aged 65 years or older (Figure 2). Compared with other age groups, the highest rate was observed in patients under one year of age, except in 2011/12. Despite similar admission rates during the first three seasons, the proportion of ≥ 65-year old patients among severe cases ranged from around 15% in 2009/10 and 2010/11 to 50% in 2011/12. In contrast, ICU admission rate for the elderly increased in 2012/13.

When compared with the age-group distribution of the general French population, children under the age of one year were over-represented among severe cases during all seasons studied. This group mainly included children under six months-old (the proportion varying from 69% in 2010/11 to 63% in 2012/13). In contrast, the 5–14 year-old group was always under-represented. Persons aged 15–64 years-old were over-represented in the 2009/10 and 2010/11 seasons and the 65 years-old and over group were over-represented in the two following seasons. The mean age of ICU cases increased significantly during the first three seasons and then declined in 2012/13 (Table 1).

The proportion of not-at-risk patients varied with the highest proportion reported in 2010/11 (35%). The proportions of pregnant women and obese patients with no other risk factors were high in 2009/10 (3%) and 2010/11 (4%). In 2011/12 and 2012/13, these values

decreased to 1% for pregnant women in both years and 1% and 5% for obese patients, respectively (Table 1). The proportion of cases vaccinated with seasonal vaccine almost doubled (29%) in 2011/12 compared with the two other seasons (13% in 2010/11 and 16% in 2012/13).

The proportion of patients with ARDS was constant over time (ca 45%), except during 2010/11 (64%). The highest proportion of patients needing ECMO (10%) or mechanical ventilation (66%) was also observed in 2010/11. The analysis was restricted to patients infected with A(H1N1)pdm09 in 2010/11 and 2012/13, two seasons where at least 21% of the circulating virus was A(H1N1)pdm09 (Table 1). It showed significantly higher proportions of patients with ARDS (68% and 57% respectively), ECMO (12% both seasons), or mechanical ventilation (70% and 69% respectively), compared with 2009/10. The p value was always less than 0.02. The proportion of patients with a severity score of 2 was significantly lower in 2011/12 (3%; 95% CI: 1–5) compared with the other seasons.

The case fatality ratio was not significantly different over time (Table 1). In the univariate analysis, it was significantly higher in patients for whom vaccination is usually recommended and patients infected with A(H1N1)pdm09, and increased with age and severity (Table 2).

Factors associated with ARDS onset and death

A significant relationship was observed between seasonal vaccination and ARDS presentation in the post-pandemic period. Therefore, the multivariate analysis was restricted to this period (Table 3).

The risk factors independently associated with ARDS were as follows:

- Age between 36 and 55 years old (adjusted OR: 1.5; 95% CI: 1.2–2.0), with age over 55 years-old as reference;
- Pregnancy with no other risk factor (adjusted OR: 3.0; 95% CI: 1.3–6.9) or obesity with no other risk factor (adjusted OR: 1.8; 95% CI: 1.1–3.0) with no risk factor as reference;

The protective factors independently associated with ARDS were as follows:

- Female sex (adjusted OR: 0.8; 95% CI: 0.7–0.98);
- Vaccination (adjusted OR: 0.7; (95% CI: 0.5–0.97);
- Infection with A(H3N2) (adjusted OR: 0.5; 95% CI: 0.3–0.6) or B strain (adjusted OR: 0.5; 95% CI: 0.4–0.6).

Since seasonal vaccination was not associated with death in multivariate analysis for the post-pandemic period (2010/11 to 2012/13), we excluded this variable and integrated the 2009/10 data in the final analysis (Table 2).

The risk factors independently associated with death were as follows:

- Severity score (score 1, adjusted OR: 4.2; 95% CI: 3.3–5.3; score 2, adjusted OR: 10.7; 95% CI: 7.4–15.4);
- Age > 55 years-old (adjusted OR: 1.5; 95% CI: 1.2–1.9).

The factors associated with a reduction in the risk of death were as follows:

- Patients for whom vaccination was not recommended (i.e. no chronic disease and age < 65 years, adjusted OR: 0.5; 95% CI: 0.4–0.6), pregnancy with no other risk factor (adjusted OR: 0.3; 95% CI: 0.1–0.7) and obesity with no other risk factor (adjusted OR: 0.4; 95% CI: 0.3–0.7);
- Age ≤ 35 years-old (adjusted OR: 0.7; 95% CI: 0.5–0.9).

There was no association between the virus type or subtypes and death. There was no interaction between age, severity score, risk factors and virus type.

Discussion

An influenza ICU surveillance system was set up in France during the 2009/10 pandemic and further developed with the active participation of ICU clinicians. In 2009, the accurate interpretation of ICU pandemic data was impossible since historical data were missing. In contrast, data obtained from the first four years of surveillance can serve as reference, showing seasonal variability in the characteristics of severe influenza cases.

The number of severe influenza cases admitted to ICUs dropped between the pandemic and the 2011/12 season and increased in 2012/13, probably reflecting the unusual length of the 2012/13 influenza epidemic (13 weeks vs 8 or 9 weeks for the other seasons). However, comparisons over seasons should be made cautiously as the level of reporting may have varied over time. Completeness of the surveillance system was estimated in two regions by capture–recapture analysis: it was 90% during the pandemic in the Provence-Cote d'Azur region [10] and 80% in 2012/13 in the Pays-de-la-Loire region [11]. There may be a tendency towards decreasing completeness over time but as surveillance remained active throughout the entire study period, with ICU wards being contacted regularly by their InVS regional office (Cire), we believe that this decline has remained limited.

Due to missing data regarding fatalities (13% over the study period), vaccination status (30% during the three years when information was collected) and influenza subtypes (23% of non-subtyped influenza A virus),

Table 3

Bivariate analysis of acute respiratory distress syndrome (ARDS) and multivariate analysis to identify risk factors associated with severe influenza-induced acute respiratory distress syndrome, France, influenza seasons 2010/11–2012/13

	Univariate analysis		Multivariate analysis			
	Complete cases	Multiple imputation (95% CI)	Complete cases (n = 880)		Multiple imputation (n = 1,839)	
			OR	95% CI	OR	95% CI
Age						
0–35 years	49%	49% (44–54)	0.8	0.5–1.3	0.8	0.6–1.03
36–55 years	67%	67% (63–71)	1.4	0.9–2.0	1.5	1.2–2.0
>55 years	50%	49% (46–53)	Ref		Ref	
Sex						
Male	57%	56% (53–60)	Ref		Ref	
Female	51%	51% (48–55)	0.8	0.6–1.1	0.8	0.7–0.98
Risk factors						
None	57%	57% (52–61)	Ref		Ref	
Chronic disease and age ≥65 years	51%	51% (48–53)	0.9	0.6–1.4	0.9	0.7–1.1
Pregnancy with no other risk factor	78%	78% (65–92)	2.2	0.7–7.7	3.0	1.3–6.9
Obesity with no other risk factor	75%	75% (68–83)	1.7	0.9–3.2	1.8	1.1–3.0
Seasonal vaccination						
No	55%	57% (54–59)	Ref		Ref	
Yes	42%	43% (36–49)	0.8	0.5–1.2	0.7	0.5–0.97
Virus						
A(H1N1)	70%	64% (61–67)	Ref		Ref	
A(H3N2)	44%	39% (34–44)	0.4	0.3–0.6	0.5	0.3–0.6
B	44%	44% (38–49)	0.4	0.3–0.5	0.5	0.4–0.6

ARDS: acute respiratory distress syndrome; CI: confidence interval; OR: odds ratio; Ref: reference value.
Significant OR (p > 0.05) shown in grey.
Data from the 2009/10 pandemic are excluded from this analysis.

we used a multiple imputation approach. No significant differences were observed between the complete case and multiple imputation analysis as shown in Table 2 and Table 3. Therefore, we are confident about the validity of the imputation procedure used and the results obtained. This process improved the power of the statistical analysis as more individuals participated in the multivariate analysis when the imputed data were used (for instance, 3,034 individuals vs 2,041 for risk factors for death study) and explained comparable OR in both approaches with larger confidence intervals in the complete case analysis. This resulted in statistically significant associations identified in the multiple imputation analysis but not in the complete case analysis.

Irrespective of the season, the A(H1N1)pdm09 virus was always over-represented among the severe cases in comparison to patients tested by GPs, reflecting its higher severity compared with A(H3N2) or B viruses. This was confirmed in the multivariate analysis, as infection with A(H1N1)pdm09 was a risk factor for presenting an ARDS.

In 2010/11, the number of ICU cases has dropped but we observed a significantly higher proportion of ARDS patients compared with the pandemic (64% vs 46%), especially when analysis was restricted to patients infected with A(H1N1)pdm09 (68% vs 46%). Similarly, in 2012/13, a significantly higher proportions of A(H1N1)pdm09 patients presented with ARDS (62%) or needed ECMO (12%) or mechanical ventilation (69%) compared with 2009/10. This finding is in favour of a persisting severity of influenza in the post-pandemic period, as observed in several countries [12-14]. It has also been observed in the past that more severe secondary waves of flu pandemics mostly involve adults with respiratory complications compared with the first wave, which mostly involve children [15,16].

Whatever the season, the 5–14 year-old group was always under-represented among the ICU cases, even during the pandemic whereas serological studies showed that they were mostly infected [17]. The 15–64 year-old group was over-represented during the pandemic and the following year when A(H1N1)pdm09 was largely circulating, reflecting the higher risk of this group to develop a severe disease when infected with A(H1N1)pdm09. By contrast, this higher risk was observed for the elderly only when A(H3N2) and B were the dominant virus.

When the virus A(H1N1)pdm09 circulated (during the 2009/10, 2010/11 and 2012/13 seasons), children

under the age of one year had the highest ICU admission rate (>4/100,000) compared with the other age groups. The ICU admission rate in this group was lower (1.1/100,000) when the virus A(H3N2) was dominant (season 2011/12). Most of the children under the age of one year (65%) were aged less than six months. As infants can be protected through maternal antibody transfer during pregnancy, the high admission rate differences among the under one-year old children, with respect to the dominant virus subtype, could reflect the fact that their mothers were better protected against A(H3N2) than they were against A(H1N1)pdm09. These observations also confirmed that this young population is at risk of severe influenza, underlying the importance of implementing interventions to improve their protection, including vaccination of pregnant women and the rest of the household, social distancing, and prompt therapeutic management when symptoms occur.

Patients exhibiting the usual conditions for vaccination recommendation (i.e. ≥65 years old or having chronic diseases) were at risk of death from influenza compared with the other patients. This vulnerability was expected and described before [18] and during the pandemics [19]. Our observation strengthens the need for better vaccination coverage among the targeted people, especially as, according to the French National Health Insurance data, vaccine coverage has declined from 60.2% in 2009/10 to 50.1% in 2012/13 [20]. It also strengthens the need for an early diagnosis and treatment of influenza-like illness in patients at risk for influenza complications. Similarly, as expected, the risk of dying increased with the severity score. In contrast, the association between the virus type and death was not significant, except for B virus which had a protective factor in the complete cases analysis. This may be due to the adjustment on severity but also to the imputation process, possibly resulting in few misclassifications of true A(H3N2) cases as A(H1N1)pdm09 cases.

In the seasons 2010/11, 2011/12 and 2012/13, A(H1N1)pdm09 was associated with ARDS. Increased incidence of ARDS due to viral pneumonia has been consistently reported during many pandemics [21]. Our finding confirms that A(H1N1)pdm09 is still a risk factor for ARDS, even after the 2009/10 wave. As described for mortality [15], increasing ARDS risk may persist for 3 to 10 years and should be taken into account when A(H1N1)pdm09 will be circulating in the following years. This risk is possibly due to the lack of immunity in the population. This hypothesis seems coherent with the protective effect of the vaccination against ARDS. However, as the data showed an association between ARDS and death, an association between vaccination and death in the post-pandemic period was expected which was not the case: vaccinated ICU patients did not seem to be better protected against death (adjusted OR: 0.9 (0.6–1.4)), even after adjusting on age and risk factors. This could be due to a lack of power of our study (216 deaths) as positive vaccination impact on mortality has regularly been described in the literature [22-24].

With 800,000 births per year in France, pregnant women are estimated to account for a slightly under 2% of the mainland population. Therefore, pregnant women with and without chronic diseases were over-represented in 2009/10 (5%) and 2010/11 (4%) among ICU cases. Estimated to represent 15% of French adults over 17 years-old in 2012 [25], obese persons (with and without associated chronic diseases) were also over-represented during the pandemic and the subsequent season (23%). The over-representation of those two groups is probably linked to the A(H1N1)pdm09 virus circulation during these two seasons (almost 100% and 50% respectively of the influenza-confirmed GP patients). The higher risk of severe influenza in pregnant women has been well documented during pandemics since 1918 [26] and this risk for patients with obesity was highlighted during the 2009/10 pandemic [26-28]. The over-representation of each group disappeared in 2011/12 and 2012/13, two seasons with low contribution of A(H1N1)pdm09 (<25%). However, among ICU cases, both pregnant women and obese patients with no other risk factor had a higher risk of developing ARDS than the other patients, even after adjusting for age and virus type or subtype. This finding supports the French vaccine recommendations which included those two groups in the influenza vaccine target in 2012.

When not associated with chronic diseases, neither pregnancy nor obesity appeared as risk factors associated with death. In the literature, increased influenza-related fatalities in pregnancy [29] and obesity [26] have regularly been observed, but this is not the case with our results. This may be explained by different choices for the reference population to estimate the risk: in the literature the reference population used was mainly the general population, whereas in our study we used patients aged 65 years old and older or with chronic diseases.

Our data regarding risk factors for death and ARDS should be interpreted with caution, as the number of variables to adjust the model was limited. In particular, we were not able to collect data on the use of antiviral therapy, which probably interferes with the estimates of the risk for severe disease and death.

In conclusion, these first four years of surveillance confirm that influenza disease may be severe. Risks for ICU admission, ARDS onset, mechanical ventilation and ECMO requirement are still higher for patients infected with A(H1N1)pdm09, even three years after the pandemic. Irrespective of the virus strain, children under one year-old are at risk for ICU admission. A higher risk was observed for adults when A(H1N1)pdm09 was circulating, and for the elderly when it was not. Vaccination seems to be protective against the onset of influenza-induced ARDS. All our data support the

importance of ICU surveillance in determining groups at risk of developing severe influenza disease and its potential for providing early warning of atypical severe patterns.

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Conflict of interest

None declared.

Authors' contributions

Isabelle Bonmarin, Emmanuel Belchior and Daniel Levy-Bruhl were mainly responsible for the design and supervision of the surveillance. Jean Bergounioux, Christian Brun-Buisson, Bruno Mégarbane, Jean Loup Chappert and Bruno Hubert were mainly involved in the data collection. Isabelle Bonmarin, Yann Le Strat and Daniel Levy-Bruhl were in charge of the data analysis. Isabelle Bonmarin drafted the paper and all the authors revised it.

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Epidemiological investigation and case–control study: a Legionnaires' disease outbreak associated with cooling towers in Warstein, Germany, August–September 2013

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Between 1 August and 6 September 2013, an outbreak of Legionnaires' disease (LD) with 159 suspected cases occurred in Warstein, North Rhine-Westphalia, Germany. The outbreak consisted of 78 laboratory-confirmed cases of LD, including one fatality, with a case fatality rate of 1%. *Legionella pneumophila*, serogroup 1, subtype Knoxville, sequence type 345, was identified as the epidemic strain. A case–control study was conducted to identify possible sources of infection. In univariable analysis, cases were almost five times more likely to smoke than controls (odds ratio (OR): 4.81; 95% confidence interval (CI): 2.33–9.93; p < 0.0001). Furthermore, cases were twice as likely to live within a 3 km distance from one identified infection source as controls (OR: 2.14; 95% CI: 1.09–4.20; p < 0.027). This is the largest outbreak of LD in Germany to date. Due to a series of uncommon events, this outbreak was most likely caused by multiple sources involving industrial cooling towers. Quick epidemiological assessment, source tracing and shutting down of potential sources as well as rapid laboratory testing and early treatment are necessary to reduce morbidity and mortality. Maintenance of cooling towers must be carried out according to specification to prevent similar LD outbreaks in the future.

Background

Legionnaires' disease (LD) results mainly from inhalation of aerosols containing the bacterium *Legionella pneumophila*, which may cause atypical severe pneumonia [1]. The infectious agent is not transmitted from person to person. The incubation period normally ranges from two to 10 days, but may be up to 20 days in rare cases [2]. A less severe form with influenza-like symptoms, also caused by *Legionella*, is known as Pontiac fever. The bacterium is found ubiquitously in freshwater environments, but man-made environments such as cooling towers provide advantageous conditions for bacterial growth [1]. Advanced age, male sex, heavy smoking and several underlying diseases have been described as risk factors for acquiring LD [3]. In 2011 *L. pneumophila* was classified as one of the highest-priority infectious disease pathogens of public health concern in Germany [4]. In the German mandatory notification system, the number of reported sporadic cases of LD in North Rhine-Westphalia (NRW) remained stable in recent years, with a mean of 115 cases per year from 2008 to 2012 [5]. The last big outbreak of LD in Germany took place in Ulm/Neu-Ulm during December 2009 and January 2010, with 64 cases, including five fatalities, and was likely to have been caused by a contaminated cooling tower [6,7].

On 14 August 2013, the regional public health office in Soest was notified of an unusual cluster of patients with atypical severe pneumonia of unknown aetiology, who had been admitted to a local hospital in Warstein. After one patient died of an atypical pneumonia on 14 August, extensive testing for legionellosis had been initiated. The first positive test result was reported on 19 August as per the German Infection Protection Act [5,8]. Between 10 and 19 August, almost 70 suspected acute LD infections were retrospectively notified to the local public health office in Soest and reported to the NRW Centre for Health. Only later did it become clear that the outbreak had started by 1 August, with 159 suspected cases in total, including 78 laboratory-confirmed cases, as of 6 September (Figure 1). Usually only a few cases per month are reported at the state level and between 2008 and 2012 a mean of 10 cases

per month were notified in NRW (range: 2–29). Of these, only three cases (one in 2008 and two in 2010) occurred in the region of Soest.

The Soest public health office consulted an expert team from the World Health Organization (WHO) Collaborating Centre for Health Promoting Water Management and Risk Communication at the University of Bonn's Institute for Hygiene and Public Health, who provided their expertise to help to investigate and eliminate the source of the outbreak. Furthermore, the Soest public health office contacted the NRW Centre for Health to support the epidemiological investigations to determine the magnitude of the outbreak in the affected region, to study the risk factors for LD and to find analytical evidence for suspected environmental sources. The German national consultant laboratory for *Legionella* at the University of Dresden was involved in laboratory confirmation and typing of patient and environmental *Legionella* strains.

Methods

Case definition

Initially cases were defined according to the German case definition as persons suffering from pneumonia, with onset of disease between 1 August and 6 September 2013 and living in or around Warstein. The German case definition includes laboratory-confirmed cases as well as cases without laboratory confirmation. The latter must both fulfil the clinical criterion and be epidemiologically linked to the outbreak, taking into account an incubation period of 2 to 10 days [8,9]. This resulted in 159 suspected cases including two fatalities with atypical pneumonia in this outbreak.

To allow comparison of this event with other outbreaks, we applied the European case definition for describing the outbreak and further analysis, which includes persons meeting the clinical criterion and at least one laboratory criterion for a probable or confirmed case, resulting in 78 laboratory-confirmed cases, including one fatality [10].

Case–control study

A case–control study was conducted to find evidence for or against potential sources. Controls were recruited from and around Warstein and were interviewed by random-digit dialling by telephone. Numbers were chosen randomly and incremented by 5 for the next call. Approximately 150 numbers could not be reached, and of the 330 people reached, 215 eligible participants agreed to be part of the study. Inclusion criteria were residence and/or stay in Warstein between 1 and 21 August 2013, as 10 August was initially assumed to be the start of the outbreak. Exclusion criteria were fever two weeks before the start of the outbreak and/or antibiotic therapy. All participants provided verbal informed consent.

Data were analysed from the 78 laboratory-confirmed cases who met the European case definition. Of these, 75 were age- (+ / – 5 years) and sex-matched with a 1:1 ratio for cases and controls.

An initial exploratory questionnaire was designed by the local health office and the NRW Centre for Health to interview patients and narrow down potential sources of infection. Cases and controls were interviewed using an amended analytical questionnaire to detect common activities, places visited and habits which might expose them to LD. The questionnaires were customised to the outbreak location, and participants were questioned about personal details, medical history and whereabouts, including proximity to locations that are typical for acquiring LD, such as whirlpools. Cases were asked to recall the 14 days preceding disease onset, whereas controls provided information for the time period since 1 August.

Environmental investigations

Relevant industrial plants were quickly identified in cooperation with the municipal public regulatory agency, and 68 cooling systems were inspected in and around Warstein. More than 880 environmental samples were collected and analysed at the University of Bonn and the consultant laboratory in Dresden, respectively (data not shown). During and after the outbreak, 26 municipal tap water samples were analysed. As of 21 August, possible contamination sources within industrial facilities had been inspected under the expertise of the environmental expert team and shut down for sampling and disinfection. Company operators were instructed not to run cooling towers or similar before proper disinfection.

Temperature, rainfall and wind data were obtained from the German Meteorological Service (Deutscher Wetterdienst, DWD) of the Federal Ministry of Transport and Digital Infrastructure.

Linear distances between cases or controls and the potential sources of the contaminated aerosols were calculated using an online calculation tool and included in the analysis [11].

Laboratory investigations

Urinary antigen was detected via Binax ELISA (Virotech Sekisui, Germany) as per manufacturer's instruction. Respiratory samples were cultured on selective and non-selective BCYE-Agar, in dilutions and/or after heat treatment for 3 minutes at 60 °C. *Legionella* DNA was detected by the Euroclone PCR assay (Virotech Sekisui, Germany) as per manufacturer's instruction. Water samples were cultured according to the ISO 11731 guideline [12]. Isolated strains were serotyped with the latex agglutination assay (Oxoid, Germany) and further by the Dresden panel of monoclonal antibodies [13]. Strains belonging to the monoclonal subtype Knoxville were further genotyped by the standard sequence-based typing method (SBT) [14]. The direct

SBT protocol for culture-independent subtyping was applied on culture negative, but PCR positive respiratory samples [14].

Statistical methods

Notification data was retrieved from the state-level SurvNet database at the NRW Centre for Health [5] and was used for analysis in addition to the data retrieved from the questionnaires. Excel (Microsoft) and SPSS 22 (IBM) were used for data management and statistical analyses. Based on univariable logistic regression and biological or epidemiological plausibility, we determined exposures that were associated with being a case by including those with $p < 0.1$ in the multivariable analysis. We conducted an unmatched forward stepwise multivariable analysis using logistic regression. Odds ratio (OR), 95% confidence interval (CI) and likelihood ratio p values were calculated in the univariable and multivariable models and values of $p < 0.05$ were considered statistically significant.

Results

Descriptive epidemiology

The outbreak comprised 78 laboratory-confirmed cases (50 males and 28 females) of LD including one fatality, who were living in the Warstein region and had an onset of disease between 1 August and 6 September 2013 (Figure 1 and Figure 2). Due to severity of illness or underlying medical conditions, not all patients could be interviewed in detail.

Suspected cases (n = 81) are indicated as blue dots and laboratory-confirmed ones (n = 78) as yellow, displayed by place of residence. Six cases (including three laboratory-confirmed) are not included in this map, because they were resident outside the displayed area. Potential sources A, B, C and D are indicated as black dots with white letters. Source D represents the local river water, which ranges from source B via C and A to D and beyond both points.

The median age of cases was 63 years (range: 19–94 years). Of 78 cases, 71 were hospitalised (91%); 12 of whom were in intensive care (17%) and 8 of whom required intubation (11%). Hospital admission dates were available for 68 cases. Median duration of hospitalisation was 9.5 days (range: 3–50 days) with 25% of patients being hospitalised for 14 or more days. Of 66 patients, 47 were on medication and/or had comorbidities (71%). All 78 cases suffered from pneumonia, 65 patients provided self-reported information about additional symptoms including fever (95%, n=62), influenza-like symptoms (52%, n=34), cough (43%, n=28), gastrointestinal symptoms (28%, n=18), headache (11%, n=7) and respiratory problems (8%, n=5). Smoking status was provided by 65 cases: 41 were smokers (63%), of whom 26 were male (63%).

The case fatality rate was 1%. In Warstein the incidence of LD infections per 1,000 inhabitants was 3.74 for male and 2.07 for female patients [15]. This incidence was higher for males than females in each age group and increased with age, especially within the male group aged older than 80 years. Nevertheless, the male-to-female ratio of 1.68:1 is lower than previously reported [16].

Surprisingly, two cases were under 40 years of age (19 and 31 years-old); both were male and living within a 4 km radius of one identified source (source A; Figure 2). One was a smoker; the other did not provide information about smoking status.

Case–control study

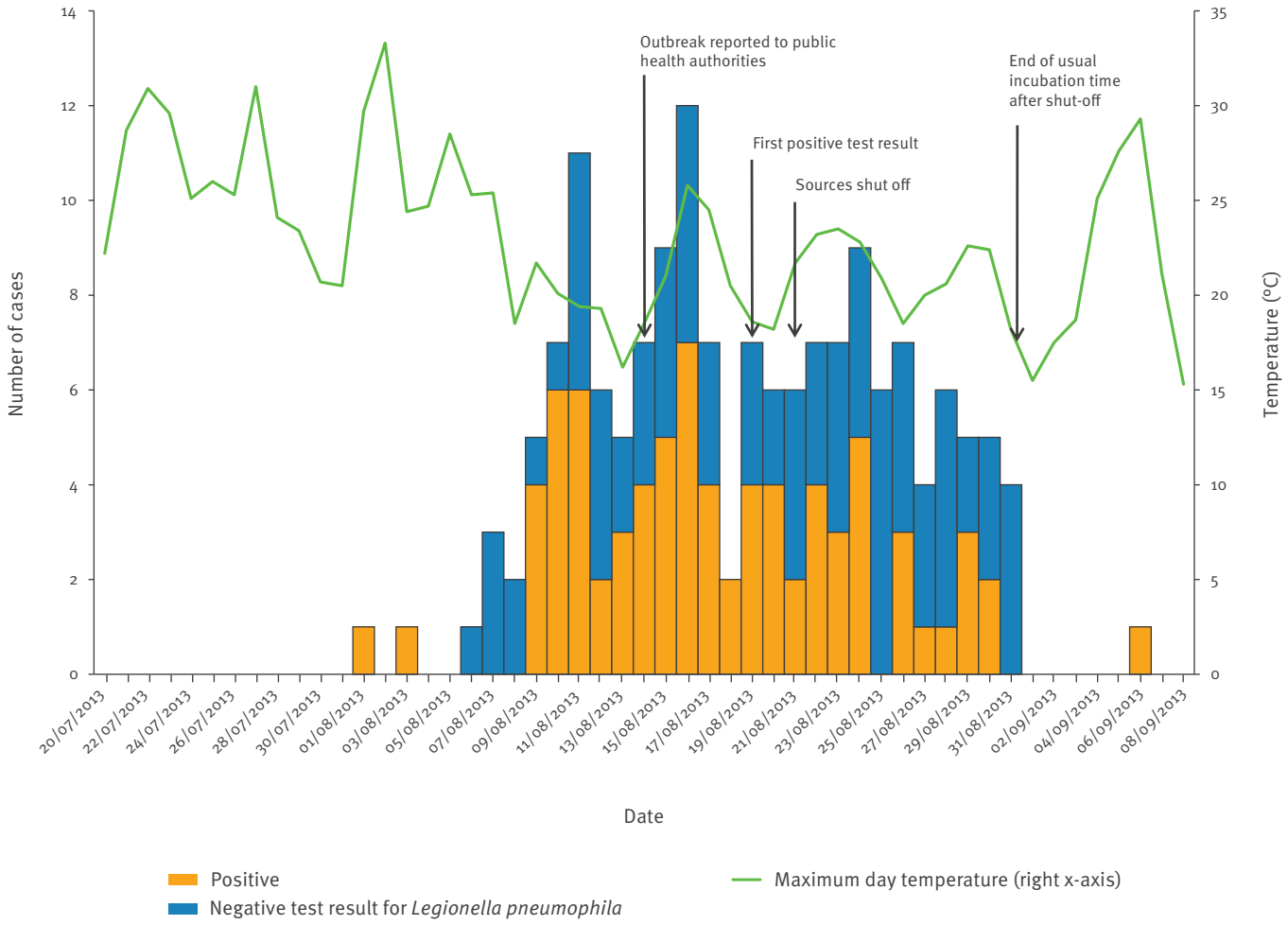
The case–control study involved 75 cases (47 male, 28 female), who contracted LD between 1 August and 6 September 2013, and 75 age- (+ / –5 years) and sex-matched controls. Median age was 63 years (range: 19–93 years) for cases and 64 years (range: 18–90 years) for controls. Within the case group, 64% were smokers (n=41 of 64) compared with just 27% of controls (n = 20 of 74). Smoking was associated with the highest odds of developing LD in univariable analysis (OR: 4.81; 95% CI: 2.33–9.93; $p < 0.0001$; Table). Although 70% of cases had underlying diseases and/or were on medication therapy (n = 44 of 63) compared with 73% of controls (n = 54 of 74), this did not prove to be a significant factor for becoming ill (univariable analysis: OR: 0.86; 95% CI: 0.41–1.80; p = 0.69; Table).

While the cases resided in and around Warstein, most of them worked or went shopping within the Warstein town area and the town centre, which comprises a small area no larger than 6 km² [17]. Shopping in Warstein resulted in apparently protective odds (univariable analysis: OR: 0.21; 95% CI: 0.082–0.54; $p < 0.001$), which probably represents only a short stay in enclosed buildings. The main connecting road between Warstein and Belecke (approximately 5 km) was also added to the data analysis, but its use was not significantly associated with LD cases. There was no evidence of infections occurring in the workplace. Most patients were retired, which is also apparent from the affected age groups. LD could not be connected to car washes, springs or other aerosol-producing areas. Very few people visited swimming pools, saunas or similar. Equally, no increased frequency of visiting dentists or local general practitioners could be observed. There was no evidence of infections being linked to large events in and around town.

Results of the linear distances between cases and controls to the potential sources A and B indicate that cases were twice as likely to live < 3 km of source A, which is located closer to the town centre than source B (Figure 2), without considering topography of the area or taking into account wind directions and strengths (univariable analysis: OR: 2.14; 95% CI: 1.09–4.2; p = 0.027); Table). The distance from source A to source B is around 5.5 km. Source A is located north and Source B south of the town, but wind directions were favourable for

Figure 1

Epidemiological curve for Legionnaires disease outbreak, Warstein, Germany, August 2013



both sources, potentially spreading aerosols into the town centre before 21 August. However, the prevailing wind direction was from the south. Compared with the distance to source A, the odds of cases living closer to source B is low, resulting in an apparently protective odds in univariable analysis (OR: 0.36; 95% CI: 0.18–0.7; p = 0.003).

In the multivariable analysis only smoking remained a risk factor for developing LD, whereas shopping in Warstein town centre seemed to be a protective factor (Table).

Environmental investigations

The epidemic strain of *Legionella* was found in four sources: two cooling towers, one sewage plant and one river water.

On 26 August the first positive result from the sampled industrial facilities was received [18], which confirmed that a cooling tower from one source (Source A; 2.84×10^5 colony forming units (cfu)/100 ml) was contaminated by several subtypes of *L. pneumophila*, with the epidemic strain representing 10% of those. In addition to source A, a second cooling tower from a different company (source B) tested positive for the epidemic strain (≤100 cfu/100 ml). Immediately afterwards the epidemic strain was also detected at the municipal sewage plant (source C; ≥ 5×10^6 cfu/100ml) as well as in the river water (source D; ≤ 3×10^4 cfu/100 ml), which consequently involved the assistance of the environmental authorities. The carbohydrate-rich wastewater of source B and the activation basin of the pretreatment plant provided an ideal environment for bacterial growth.

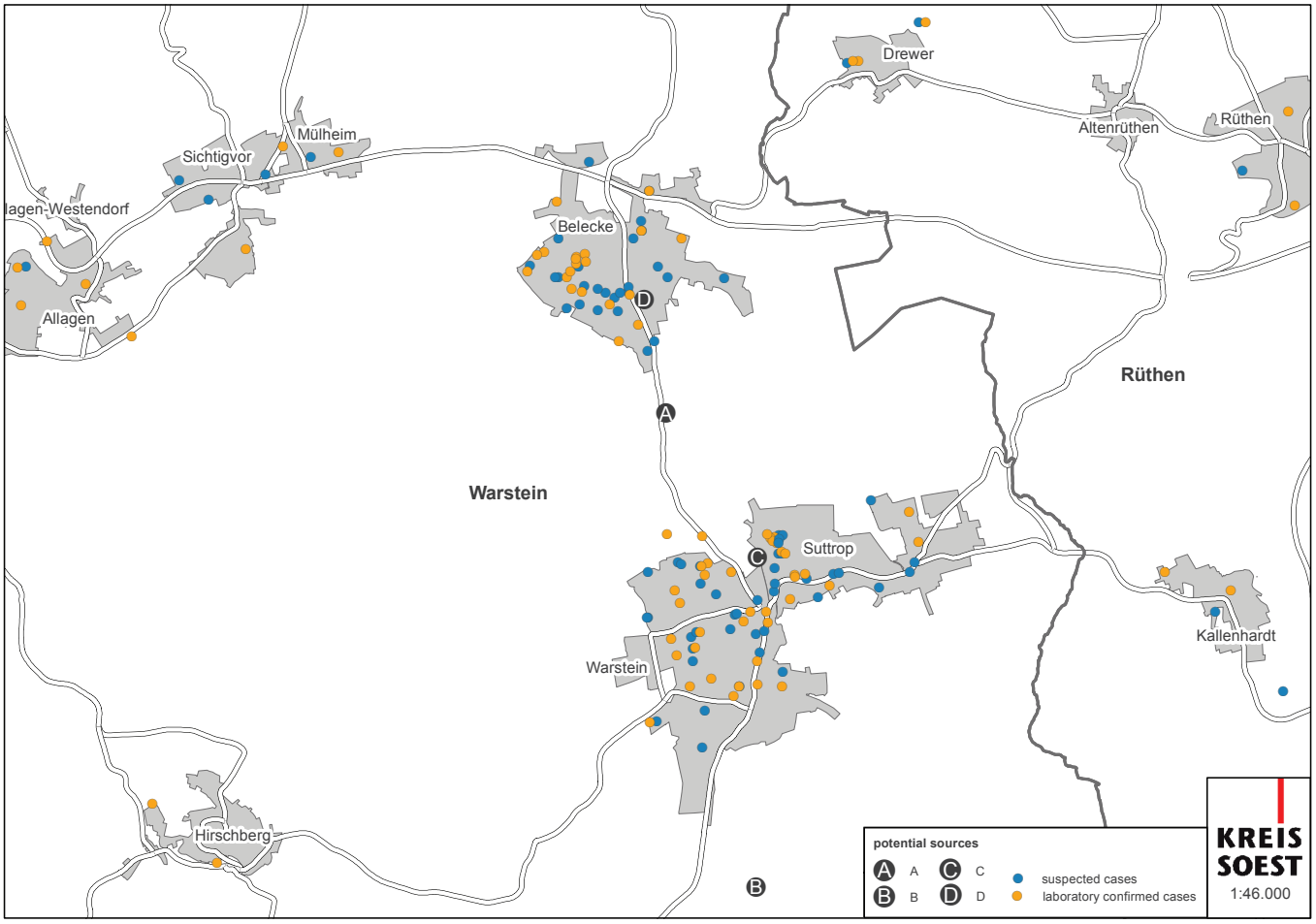
During and after the outbreak 26 municipal tap water samples were analysed, all of which were negative.

Prior to the outbreak there were 12 warm days (maximum temperature ≥ 25 °C) between 21 July and 7 August (Figure 1), which may have helped initiate the spread of *L. pneumophila* from cooling towers. Warm weather conditions with temperatures from 25 °C to 30 °C lasted until the first week of August.

Wind direction data was dichotomised and roughly classified as mainly from a northerly (270 ° to 360 ° and 0 ° to 89 °) or southerly (90 ° to 269 °) direction. Between 21 July and 20 August, 78% of the hourly wind

Figure 2

Geographical distribution of cases, Legionnaires' disease outbreak, Warstein, Germany, August 2013 (n=78)



Suspected cases are indicated as green dots and laboratory-confirmed ones as red, displayed by place of residence. Six cases (including three laboratory-confirmed) are not included in this map, because they were resident outside the displayed area. Potential sources A, B, C and D are indicated as black dots with white letters. Source D represents the local river water, which ranges from source B via C and A to D and beyond both points.

direction measurements show wind from the south, with eight days showing wind only from south.

Laboratory investigations

On 19 August the local public health department received the first positive laboratory result for *L. pneumophila* serogroup 1 sampled from a patient.

L. pneumophila, serogroup 1, subtype Knoxville, sequence type (ST) 345, was identified as the epidemic strain of this outbreak, and could be isolated from seven patients as well as several environmental samples from two cooling towers, a municipal sewage plant and a river water source in Warstein [13,19]. Complete or partial sequences compatible to ST 325 were obtained from three further cases.

One culture-confirmed case with disease onset on 6 September was included in the outbreak as the presence of the epidemic strain could be verified for this person, suggesting an unusually long incubation period, which has been observed to be 20 days in exceptional cases [2].

Outbreak management

The local health authorities conducted commendable press work with regular updates on the situation and public information. In addition to daily press releases, a helpline for the general public was set up by the Soest local health office.

Public health measures were discussed during several teleconferences between responsible authorities and expert teams. In addition, the NRW Centre for Health updated the other state health authorities in Germany and the Robert Koch Institute via regular epidemiological teleconferences about the outbreak. The Robert Koch Institute released a short summary in their weekly epidemiological bulletin to inform public health authorities in Germany about the outbreak and to promote quick and targeted diagnostics as well as therapy for suspected cases possibly linked to Warstein [20].

Table

Univariable and multivariable analysis of probable exposure factors, Legionnaires' disease outbreak, Warstein, Germany, August–September 2013

Exposure	Cases			Controls			Univariable		Multivariable	
	Exposed	Total	%	Exposed	Total	%	OR (95% CI)	p	OR (95% CI)	p
Male sex	47	75	62.7	47	75	62.7	1	1	[a]	
Drugs and/or Comorbidity	44	63	69.8	54	74	73.0	0.86 (0.41–1.80)	0.69	[a]	
Smoker	41	64	64.1	20	74	27.0	4.81 (2.33–9.93)	<0.0001	5.11 (2.31–11.32)	<0.0001
Attending event	7	59	11.9	5	75	6.7	1.89 (0.57–6.27)	0.30	[a]	
Shopping in Warstein	41	61	67.2	68	75	90.7	0.21 (0.08–0.54)	<0.001	0.18 (0.06–0.50)	<0.001
Travelling via main road	40	57	70.2	48	74	64.9	1.28 (0.61–2.68)	0.52	[a]	
Distance to source A< 3 km	52	75	69.3	37	72	51.4	2.14 (1.09–4.20)	0.027	[b]	
Distance to source B< 3 km	25	75	33.3	42	72	58.3	0.36 (0.18–0.70)	0.003	[b]	

CI: confidence interval; OR: odds ratio.

[a] Not considered for multivariable analysis (p ≥ 0.1).

[b] Not included in the final model by the stepwise forward variable selection procedure.

One confirmed case of LD was reported outside of Warstein with a possible connection to the outbreak, but could not be linked epidemiologically. Another person living in Sweden was suspected to be suffering from LD after visiting Warstein during the outbreak [18]. This person had already been interviewed and had neither pneumonia nor other typical LD symptoms and thus no laboratory testing had been initiated. The NRW Centre for Health tracked this probable case via the Robert Koch Institute and the national focal point in Sweden, but did not reveal an official notification of LD within the country of residence; hence this person was not linked to the outbreak.

As a measure of infection prevention (according to article 16 of the German Infection Protection Act [21]) the local authorities decided on 27 August to cancel a major event which was expected to attract 150,000 visitors. Intensified public health measures were effective as of 30 August, when the local health authorities announced that unnecessary travel to Warstein should be avoided until the definitive source had been identified and that people developing symptoms should seek medical attention. The public health recommendations ended after completion of protective measures at the environmental sources on 18 September.

Discussion

Here we describe the largest community-associated outbreak of LD in Germany to date. This outbreak resulted in 159 suspected cases including 78 laboratory-confirmed cases. Several other previous outbreaks within Europe, including those in Spain, the United Kingdom and the Netherlands, caused larger numbers of LD cases compared with the outbreak in Warstein [22-24]. We cannot exclude the possibility that suspected cases without laboratory confirmation were suffering from something other than LD. However, due to surveillance data and the hospitalisation of a large number of people, an unusual cluster of LD was suspected. Hence, all cases with pneumonia were initially linked epidemiologically to the outbreak. To make our analysis applicable to other countries, the European case definition was applied, so our analysis involved 78 laboratory-confirmed cases including one fatality.

The case–control study helped to exclude potential sources of infection. The main results reveal a higher incidence rate within the male population. Also, smoking was a high risk factor for becoming infected. Data analysis of the questionnaire showed that movement of both cases and controls was very limited: with only few reported travelling while some had not left their homes at all. Immobile cases were most likely infected via airing their homes, which is not unusual during hot summer periods. Shopping in Warstein resulted in apparently protective odds, which could be due to being indoors and not exposed to aerosols outside. Apart from that it gives evidence against the shopping centre area being a source of infection, a possibility which had been considered at the beginning of the outbreak. Although the case–control study shows a higher risk for LD for people living closer to source A, this does not exclude people living further away, who may still have visited the town centre and suffered from LD.

More than one potential source contaminated by the outbreak strain was identified and although no definite conclusion could be made, industrial cooling towers belonging to two companies were most likely responsible for this outbreak. Due to the shutting off of potential sources, together with the topographic location of Warstein, further spread and transmission of bacteria could be contained quite rapidly.

As in previous outbreaks, the epidemic strain reacted with the monoclonal antibody Mab 3–1. Such strains have a higher hydrophobic surface in comparison with other *Legionella* strains, which might be the reason for the high transmissibility and survival in aerosols [25]. Nevertheless, according to the SBT database for *L. pneumophila* the outbreak strain was previously associated with only eight sporadic cases of pneumonia worldwide and is therefore not a very common cause of *Legionella* pneumonia [14].

Source A could not be solely or primarily responsible for the magnitude of this outbreak, due to the height, size and properties of its cooling tower. Also, source A was contaminated by several subtypes of *L. pneumophila,* only 10% of which were the epidemic strain. Confirmation of the outbreak strain of *L. pneumophila* in several sources led to the hypothesis that source B contaminated source C via partially treated sewage, which then drained treated wastewater into source D. A series of events in combination is most likely responsible for the outbreak as source A was almost certainly contaminated using water from source D to run their cooling tower. In addition, wind conditions were favourable for spreading contaminated aerosols via both cooling towers in source A and B. However, source B may have been responsible for some cases near source A, as the predominantly southerly wind could have transported the pathogen 7 to 10 km by aerosols from source B into the region <3 km around source A [26]. Apparently protective odds for the region <3 km around source B support a further transmission of aerosols. It should also be noted that the area around source B is mostly uninhabited, including only a small part of the town centre north of the source.

Sewage plants are known to be a source for L. *pneumophila* and have been described as a source of LD infections [27]. During an outbreak of LD in Norway, a biological treatment plant was identified as an indirect infection source, contaminating an air scrubber, which acted as an infection vehicle. Eight of nine employees at this plant were seroresponders with a working distance from the plant less than or equal to 200 m [28], similar to our observations regarding exposure distance to aerosols of the treatment plant (Source C). However, no employees of the local sewage plant came down with symptoms or disease in our study.

The low case fatality rate of 1% compared with the European mean of 10% [16] may be mostly due to immediate clinical management of patients at the local hospitals in Warstein as well as the effective public health measures from the health department in Soest. Still, the capacity of the local hospital was stretched to its limits, so that patients had to be allocated to surrounding hospitals. The immunochromatographic urinary antigen tests initially used were not sufficiently sensitive, and so at the start of the outbreak many antigen tests were false negatives. Retesting of urine samples via a more sensitive method (ELISA) was subsequently performed for more than 500 samples at the consultant laboratory and thus the number of laboratory confirmed cases increased during and after the outbreak. Nevertheless, only 78 of 159 patients had a positive test result, which may be due to rapid initiation of therapy. Fields et al. reviewed studies showing that antigen was detected in more than 80% of patients between day 1 and 14 after onset of symptoms and 100% after day 14 up to more than 300 days in exceptional cases. However, in some patients, who had been on therapy for four days, antigen was no longer detectable [1]. Immediate initiation of therapy may have been one reason for the low number of positive test results during this outbreak, as well as delayed utilisation of another more sensitive test. Moreover, concentration of urine samples may lead to increased sensitivity [1]. Also, test sensitivity depends on severity of infection [29].

The outbreak in Warstein was attended by a series of uncommon events. Involvement of more than one source made tracing difficult. Cooling towers have previously been described as posing a risk for LD outbreaks, and so the search for the source focused on relevant industrial facilities. Besides cooling towers at big industrial facilities, other sites should be considered, such as environmental locations (e.g. river water as a water source for cooling towers) and biological waste plants. Furthermore, companies and industrial workers should be better trained in maintenance of their facilities, so as to avoid the occurrence of similar outbreaks [30].

Decision-making on public health measures must be supported by all the relevant authorities and should stay in effect until all potential sources have been closed. Because of the outbreak, a large public event in Warstein (150,000 visitors expected) was cancelled. According to LD case numbers at that time, it was estimated that had the event gone ahead, there would have been around 800 additional suspected cases and consequently further fatalities. This reinforced the recommendation not to visit Warstein unless necessary. The main issue leading to the decision to cancel this event was the risk of elderly visitors in particular being infected and receiving late or untargeted treatment from their local general practitioners, which could have resulted in more severe illness or even more deaths.

One limitation of our study is that the outbreak was recognised and notified quite late and so there were many retrospectively notified suspected cases and

fewer laboratory-confirmed ones. Nevertheless, applying the German case definition, 159 suspected cases were included in this outbreak on a national level. Considering that the true incidence of LD cases in Europe is estimated to be much higher than reported [2] and also that cases in this outbreak were probably underdiagnosed, the German case definition seemed suitable for this outbreak situation, making it likely that no cases were missed.

This study demonstrates how important a quick assessment of the situation is to limit morbidity and mortality rates. Rapid effective testing and early clinical management are as important as the source tracing in such an outbreak, as well as seeking cooperation and using the expertise of all responsible authorities including political ones. Correct identification and prompt interview of cases and controls may help to exclude possible sources and focus on relevant exposure sites. Most importantly, a collaborative approach involving several departments with different expertise and areas of responsibility proved to be very effective in quickly containing this outbreak.

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Conflict of interest

None declared.

Authors' contributions

AM and AJ drafted the manuscript and IDH critically reviewed the paper. AJ, AM and IDH designed the case-control study, AM and AJ performed the epidemiological analysis and interpreted the results. ME and SP were responsible for source tracing, environmental laboratory analysis and risk assessment, and CL for typing clinical and environmental strains of legionella. Recommendation of public health measures was discussed by FR, AB, IDH, AJ, ME. AJ, AM, IDH, FR and AB interpreted notified cases and epidemiological relevance.

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Incidence of invasive meticillin-resistant *Staphylococcus aureus* infections in Germany, 2010 to 2014

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Voluntary surveillance systems in Germany suggest a recent decline in the incidence of infections (subsequent to at least 2010) with meticillin-resistant *Staphylococcus aureus* (MRSA) from various types of specimens and settings. We asked whether this decline is reflected by data from the mandatory national surveillance system for invasive MRSA infections. Our analysis is based on the population in Germany in 2010 to 2014. Cases were identified from passive reporting by microbiological laboratories of the diagnosis of MRSA from blood culture or cerebrospinal fluid. Respective clinical data were subsequently added to the notification. We calculated risk ratios (RR) between consecutive years, stratifying cases by sex, age and federal state of residence. The national incidence increased from 4.6 episodes per 100,000 persons in 2010 to 5.6 in 2012 (2011 vs 2010: RR: 1.13, 95% confidence interval (CI): 1.08–1.18; 2012 vs 2011: RR: 1.08, 95% CI: 1.04–1.13). It stagnated at 5.4 per 100,000 in 2013 (RR: 0.97, 95% CI: 0.93–1.01) before declining to 4.8 in 2014 (RR: 0.88, 95% CI: 0.84–0.91). This trend was observed in most, but not all federal states and strata of sex and age groups. Only 204 of 20,679 (1%) episodes of infection were notified as belonging to an outbreak. Our analysis corroborates previous findings that the incidence of invasive MRSA infections in Germany may be declining.

Introduction

In 2013, 12.8% (95% confidence interval (CI): 12–14) of *Staphylococcus aureus* isolates from blood culture in Germany were found to be resistant to meticillin in laboratories submitting data to the European antibiotic resistance surveillance network (EARS-Net), placing Germany below the European average of 18% [1]. The prevalence of meticillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia is now within the middle lower range of those reported in Europe.

MRSA infections in Germany are thought to be mainly healthcare-associated (HA) with only a small proportion, which are community-associated or livestock-associated [2]. HA-MRSA especially affects persons above the age of ca 50 years. Due to unknown reasons, the prevalence of HA-MRSA is higher among men than women as well as in the northern than southern states of Germany [3,4]. In addition, livestock-associated MRSA may account for ca 8% of MRSA isolated from blood cultures in regions with a high density of swine farming [5].

Analyses from voluntary laboratory- and hospital-based sentinel surveillance networks for different types of specimens and settings suggest a decline in the incidence of MRSA infections in Germany, subsequent to at least 2010 [1,2,6,7]. These networks are not part of the mandatory reporting system and are not representative for all of Germany. Many of them, such as the EARS-Net, report data solely on the proportion of meticillin resistance among all tested *S. aureus* isolates, which are difficult to translate to incidences. We therefore asked whether or not a similar decline could be seen in the statutory surveillance system for invasive MRSA infections, which was introduced in 2009 and allows the direct estimation of incidences [8].

Methods

Study design

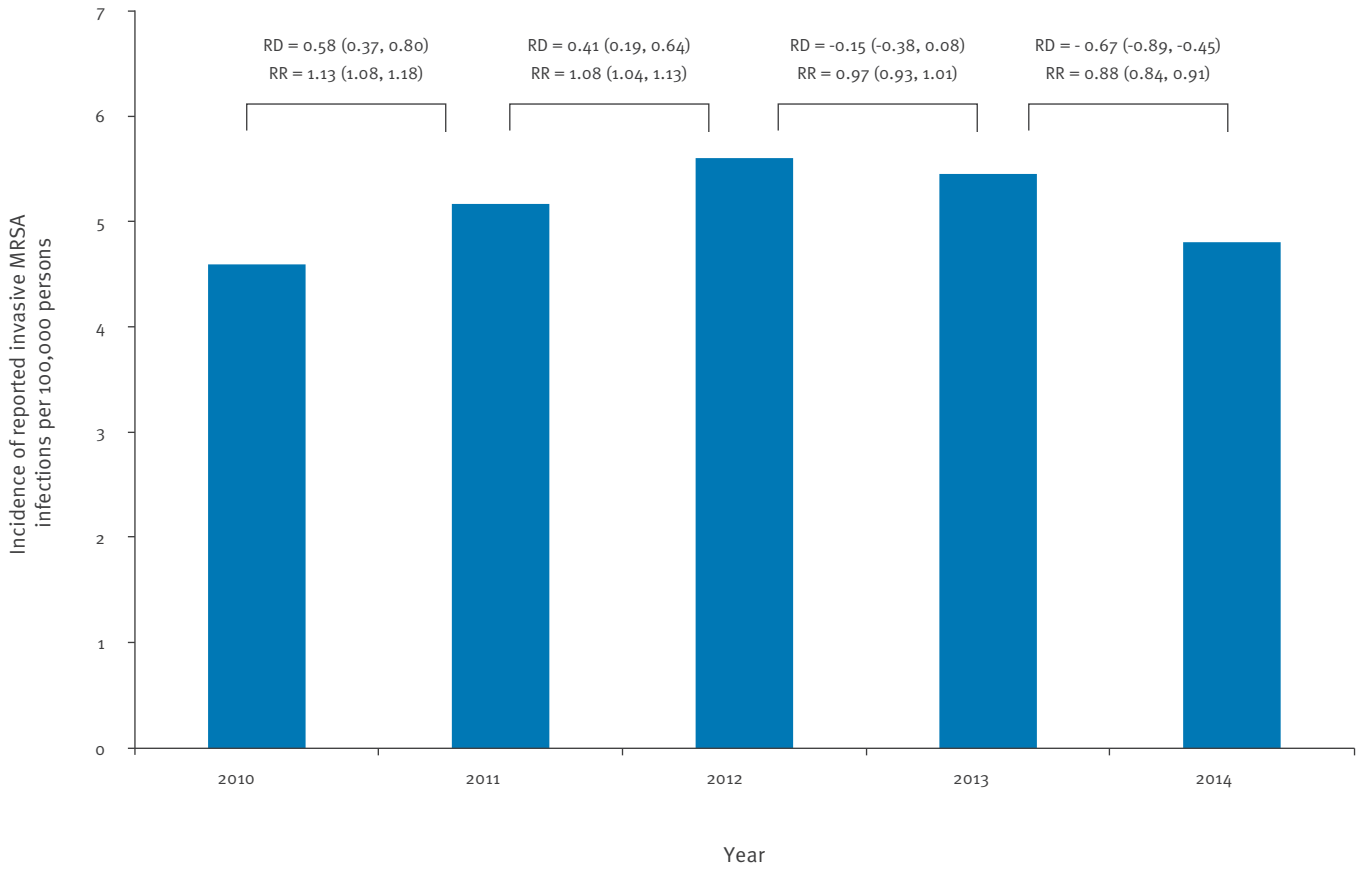
We conducted a retrospective cohort study including the total of the population in Germany. Cases were identified by the mandatory notification system for invasive MRSA infections, which was introduced in 2009. We limited the analysis to the period from 2010 to 2014, since 2010 was the first year with a full year of data collection [8]. As possible confounders or effect modifiers we included sex, age and area of cases' residences.

Case notifications

Microbiological laboratories are required to notify patients with MRSA positive blood culture or samples from cerebrospinal fluid (CSF) to the local health authorities. Valid tests included in the case definition

Figure 1

Annual incidence of episodes of invasive meticillin-resistant *Staphylococcus aureus*, Germany, 2010–2014 (n=20,679)



MRSA: meticillin-resistant *Staphylococcus aureus*; RD: risk difference; RR: risk ratio.

The numbers in parentheses indicate 95% confidence intervals. Only notifications marked as fulfilling the reference definition are included.

and reference definition (used for this analysis) are culture combined with meticillin sensitivity testing or with detection of the *MecA* gene, e.g. by polymerase chain reaction (PCR). The local health authorities subsequently add respective clinical data to these notifications and transmit them via the state office to the national surveillance database, which is maintained at the Robert Koch Institute. The German Protection against Infection Act mandates transmission to this database within two working days after diagnosis. To avoid multiple notifications of the same patient, subsequent notifications are excluded if reported within two weeks [9].

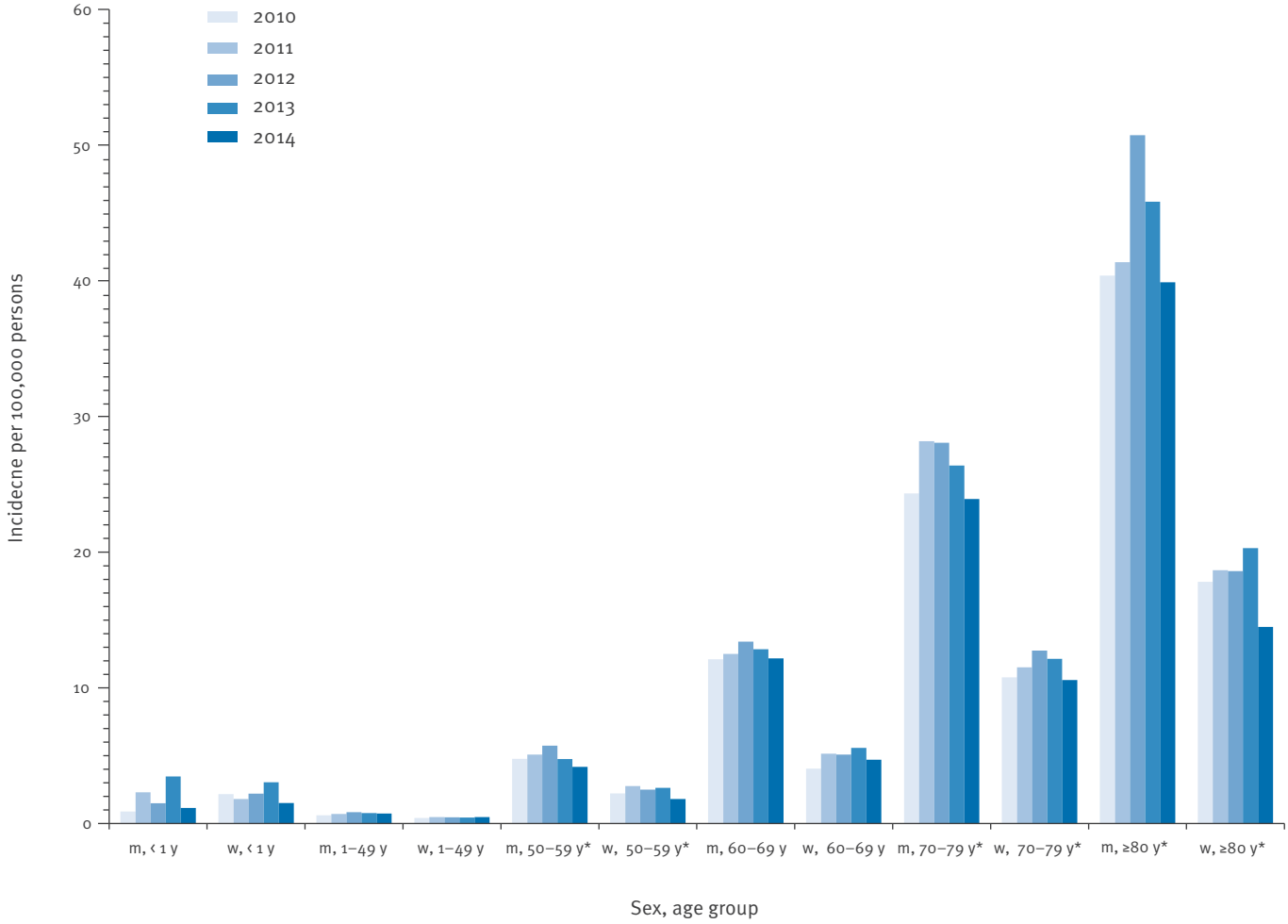
Data on the following case characteristics are transmitted to the Robert Koch Institute: sex, month and year of birth, the district of the patient's home address, the place of possible exposure, the date of the notification, the date of disease onset, the laboratory methods used for diagnosis (type of specimen and test used), whether or not the case fulfils the reference definition (independently of other variables), clinical symptoms, date of death and whether or not the death is due to an MRSA-infection, hospitalisation dates, whether or not the case is connected to an outbreak. The clinical case definition for invasive MRSA infections, as used by the German surveillance system, requires the patient to have at least one of the following symptoms: fever (≥38.5°C), signs of endocarditis, meningitis, meningoencephalitis, meningomyelitis, pneumonia or sepsis. However, the presence or absence of clinical characteristics does not change the necessity to notify this case to the authorities.

Since August 2011, information on HA infection outbreaks of epidemiologically-linked nosocomial (symptomatic) infections are additionally transmitted from local public health authorities to federal states and from there to the Robert Koch Institute [8,10]. In contrast to the notification of invasive MRSA infections, these notifications include information on the number of all affected patients; thus cases with non-invasive MRSA infection such as colonised cases are also included.

Data of notifications of invasive MRSA infections were extracted from the national surveillance database at

Figure 2

Incidence of notified episodes of invasive meticillin-resistant *Staphylococcus aureus* infections per 100,000 persons stratified by age, sex and year of notification in Germany, 2010–2014 (n=20,667) [a]



M: men; w: women; y: years-old.

The asterisk marks significant differences ($p < 0.05$) between 2012 and 2014. Only notifications marked as fulfilling the reference definition are included.

[a] 12 cases of 20,679 were excluded due to missing data for sex or age.

the Robert Koch Institute (SurvNet3@RKI) as collected up to 1 March 2015.

Population denominator

Aggregated population data in strata of age, sex, German federal state and calendar year (31 December of the preceding year, i.e. 2009 to 2013) were downloaded from the national institute of statistics (www.destatis.de) on 7 October 2014.

Statistics

We used chi-squared tests to compare categorical variables and Kruskal-Wallis tests to compare continuous variables between years. To calculate the annual incidence of invasive MRSA infections we categorised infections by the year of notification based on the epidemiological week number rather than calendar years. We then divided their number by the population at risk, i.e. the population on 31 December of the preceding year. We used chi-squared statistics to calculate confidence intervals around risk differences and risk ratios (RR) and to test for differences in incidence between years. We classified age in the categories shown based on the age distribution of the cases. We chose German federal state as the geographic level for analysis since a finer break down would have resulted in many empty or sparsely populated cells. For the differentiation in rural and urban areas we relied on the official German categorisation in urban ('kreisfreie Stadt') or rural districts ('Landkreis'). Some districts are excluded, since they comprised urban areas together with the surrounding rural area. For notifications with several places of a possible exposure we only included one in the analysis, prioritising foreign countries over Germany and other German states over those that equalled the notifying state. Since earlier software

products automatically set the place of exposure to the notifying state, the answer 'unknown' and 'same state as notification' were grouped together as one category. To assess the presence of effect modification we used the Mantel-Haenszel test for homogeneity. Throughout the analysis, tests were considered significant if the p-value was below 0.05.

We analysed the data with Stata SE13 (College Station, Texas, US). Maps were produced by Regiograph Planing Version 13 (GFK GeoMarketing GmbH, Germany).

Reporting

We followed the recommendations given in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [11].

Ethics

The study was based on the statutory case notifications as mandated by the German Protection against Infection Act. These data were available in anonymised form at national level. Ethical approval for analysis of such surveillance data are not required according to the Medical Association's professional code of conduct.

Results

Case characteristics

Between 2010 and 2014 there were 20,764 notifications of invasive MRSA infections in Germany. Eighty-five (0.4%) of them were excluded, since the reference definition was not fulfilled, resulting in a final study population of 20,679 notifications.

The characteristics of the included cases by year of notification are shown in Table 1 and 2. While the age distribution of the notified cases remained remarkably stable over the years, there were a number of other small but statistically significant changes. These include changes in the distribution of cases between the sexes, the German federal states, rural and urban areas, the type of specimen used for diagnosis, the proportion fulfilling the clinical case definition, several clinical symptoms, the proportion hospitalised, those with dates on disease onset and hospitalisation, those with a hospital onset of the infection, the mortality and case fatality ratios. Notable is an increase in the proportion and absolute numbers of patients with clinical signs of sepsis between 2010 and 2013, as well as those with sepsis due to a central vein catheter or other invasive access. The absolute numbers in both categories of cases however declined again in 2014 as compared with 2013.

Only few notifications of invasive MRSA infections were marked as being associated with a nosocomial outbreak (such notifications are independent of the transmission of data on nosocomial outbreaks as introduced in 2011). These amounted to a total of 204 of 20,679 (1%) for the whole study period, 37 of 3,754 (1%) for 2010, 37 of 4,227 (1%) for 2011, 31 of 4,485 (1%) for 2012, 40 of 4,372 (1%) for 2013, and 59 of 3,841 (2%) for 2014 ($p = 0.002$).

Remarkably, in patients with known disease onset and hospitalisation dates, few episodes (39%) of illnesses due to invasive MRSA occurred while patients were within the hospital. HA-MRSA infection was defined as disease onset later than the second day of hospitalisation but before or on the day of discharge.

The case fatality rate was 8%, with small but significant variations between the years. The cases with known dates of death and disease onset appeared to have a relatively short time between illness onset and death, with a median of seven days (interquartile range: 3 to 18). This short period can be explained by an underreporting of later deaths due to an undefined time point for follow-up by the public health department.

Possibility of recurrent infections

Even though unique personal identifiers are not included in the final dataset, we tried to assess the frequency of persons with repeated episodes of MRSA infections per year. We analysed the dataset for repetitions of the same combination of birth month and year, sex, district and notification year in the dataset. Over all five years (n=20,679 cases), we found 490 (2%) of these repetitions per year, suggesting that more than one episode of invasive MRSA infection in the same patient was rare. Of note, 71 (14%) of the repeated notifications were within two weeks of a previous notification, allowing for the possibility of double entries of the same episode.

Trends in the incidence of invasive meticillin-resistant *Staphylococcus aureus* infections

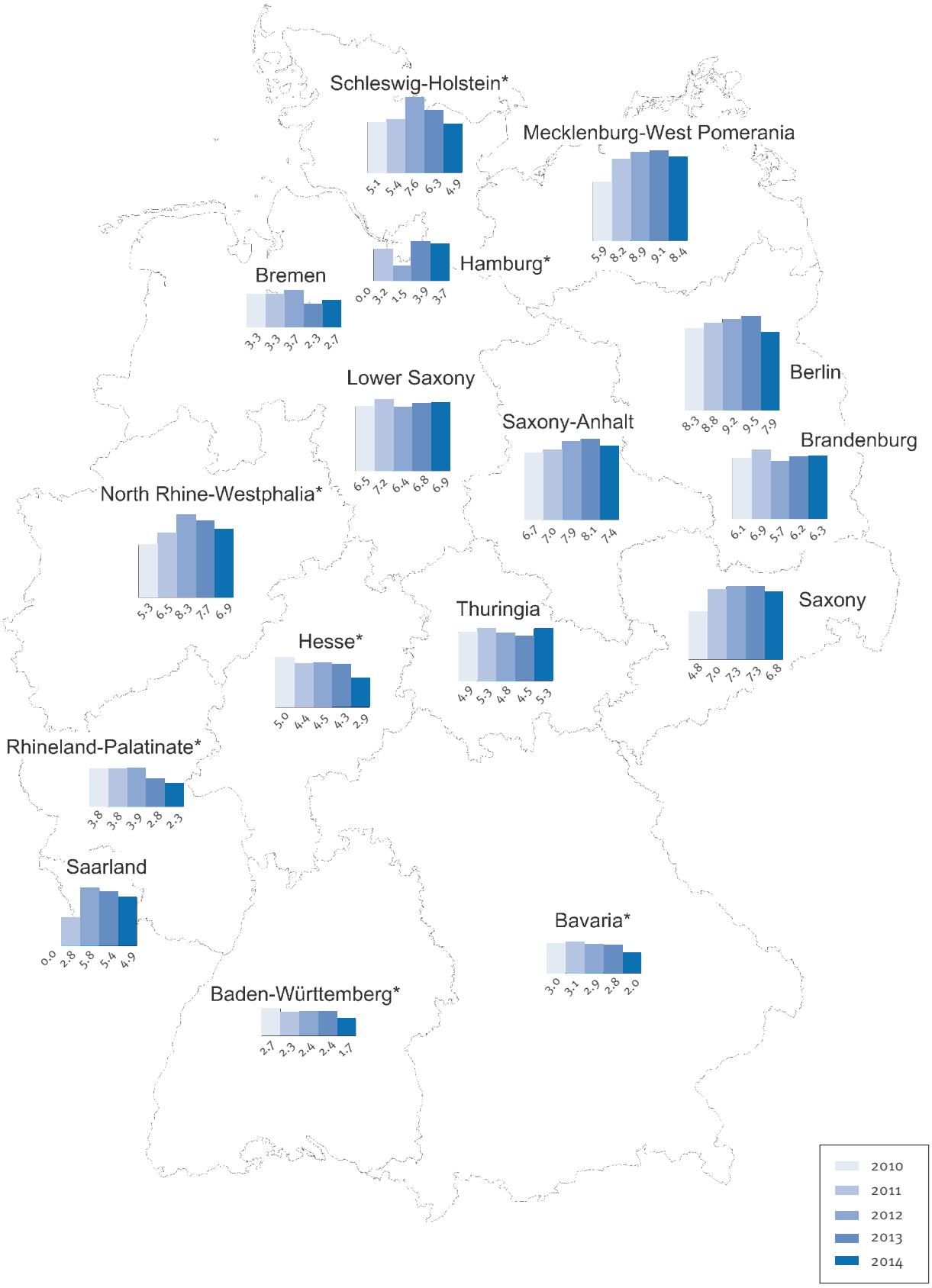
The incidence of invasive MRSA infections in Germany increased from 4.6 episodes per 100,000 persons in 2010 to 5.6 per 100,000 persons in 2012. With 5.4 episodes per 100,000 persons, it remained high in 2013, before dropping to 4.8 episodes per 100,000 persons in 2014. The risk difference and risk ratios (RR) between consecutive years are significant, with the exception of the years 2012 and 2013 (Figure 1). Results did not change appreciably when including all notified cases regardless of reference definition or when restricted to those specifying the origin of the sample as either blood or CSF (data not shown).

The effect of age, sex, state, and urban vs rural areas

The incidence is increasing with age, starting at ca 50 years of age (Figure 2). It was nearly double among men compared with women (RR: 1.79, 95% CI: 1.74–1.85), with the exception of children and adults below 50 years of age. It differed by a factor of ca four between federal states, with generally higher incidences in northern states (Figure 3) as well as in urban vs rural areas (Figure 4).

Figure 3

Incidence of notified episodes of invasive meticillin-resistant *Staphylococcus aureus* infections per 100,000 persons by federal state and year of notification, Germany, 2010–2014 (n=20,674)[a]

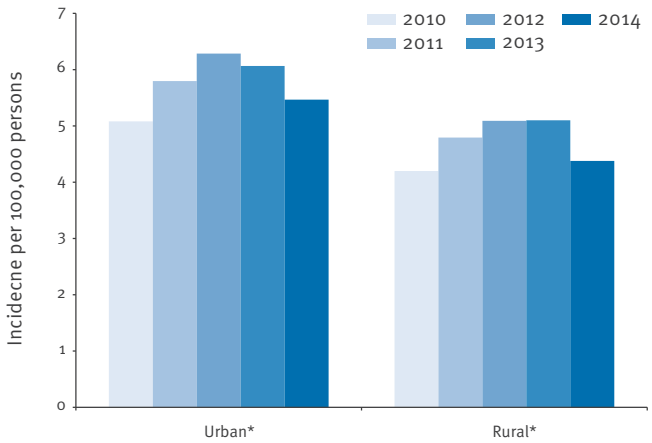


The asterisk marks significant differences ($p < 0.05$) between 2012 and 2014. Only notifications marked as fulfilling the reference definition are included.

[a] Five cases of 20,679 were excluded due to missing data.

Figure 4

Incidence of notified episodes of invasive meticillin-resistant *Staphylococcus aureus* infections per 100,000 persons according to year of notification and urban or rural area, Germany, 2010–2014 (n=20,035)[a]



The asterisk marks significant differences (p<0.05) between 2012 and 2014. Only notifications marked as fulfilling the reference definition are included.

[a] 644 cases of 20,679 could not be attributed to either rural or urban areas.

A decline in the MRSA incidence between 2012 and 2014 is found for most but not all strata of age, sex, and state, as well as for rural and urban areas (Figure 2 to 4). For example the decrease in incidence from 2013 to 2014 is seen in all strata of age and sex, except for women between 1 to 50 years of age (test for homogeneity: p=0.01). Similarly, some states had even an increase in incidence in 2014 (Brandenburg, Bremen, Lower Saxony, Thuringia) or in 2013 (Brandenburg, Berlin, Hamburg, Lower Saxony, Mecklenburg-West Pomerania, Saxony-Anhalt) as compared with the preceding year (test for homogeneity for 2014 vs 2013: p=0.005; for 2013 vs 2012: p=0.003). These differences are not due to confounding since the age structure in Germany remained relatively stable during the time of the analysis and since the stratified and crude Mantel-Haenszel estimates were similar.

Outbreaks

As part of the notification for HA outbreaks, which are independent of the notification of invasive MRSA infections, a total of 95 outbreaks of MRSA were reported for the years 2012 to 2014. These comprise colonisation and all types of MRSA-infections, not only invasive infections. In 2012 there were 27 outbreaks comprising 120 cases (among those 98 infected, 20 colonised und 2 unspecified), 30 outbreaks with 143 cases (71 infected, 54 colonised and 18 unspecified) in 2013 and 38 outbreaks with 209 cases (79 infected, 103 colonised and 27 unspecified) in 2014.

Discussion

This is the first trend analysis of the incidence of invasive MRSA infections including the complete population in Germany. We found that the annual incidence of notified invasive MRSA infections increased from 2010 until its peak in 2012 to 2013 before declining again in 2014. We additionally observed statistically different trends between German federal states and to a lesser extent between some categories of age and sex, suggesting different trends at local level and possibly for certain patient groups.

As with all passive surveillance systems, underreporting and effects due to changes in the reporting compliance cannot be excluded. Especially during the first years after the inclusion of MRSA in the national surveillance system underreporting and the number of data errors may have been high due to a lack of training and due to technical problems [12]. We therefore think that the increase in 2011, and possibly in 2012 may in part be due to a surveillance artefact and it may also explain changes in clinical symptoms, such as the increase of clinical sepsis. However, given an assumed stabilisation of the surveillance system we believe that the decline in 2014, even though small, is likely to be real. The decline in 2014 includes cases with clinical sepsis as well as those with sepsis and central vein catheter or other invasive access, which further corroborates this interpretation.

Germany has done much to control its MRSA epidemic. This includes the implementation of a national antibiotic resistance strategy (DART, 2008 updated 2015) (www.bmg.bund.de), the establishment of regional networks to combat multiresistant bacteria (since 2004 with the support of the Robert Koch Institute) [13], the conduction of various screening programmes [14-16], the adaption of respective clinical guidelines (http://www.awmf.org), the development of antibiotic stewardship programmes, additional legislation on federal state levels, recommendations by the Robert Koch Institute concerning hospital hygiene (www.rki.de) and the establishment of various surveillance systems such as the mandatory reporting for invasive MRSA infections in 2009 and the antibiotic resistance surveillance (ARS) in 2007 [7]. It is therefore tempting to think that these interventions had some effect on the incidence of invasive MRSA infections. However, surveillance data are rarely suitable to prove causal links. We cannot exclude other causes, such as changes in the frequency of testing and biological mechanisms [17]. For example with additional testing, which is likely to have occurred due to an increased awareness of the possibility of antibiotic resistance, the number of detected and reported cases is likely to increase [18]. A biological factor possibly contributing to the decrease of MRSA in Germany is the reduction of epidemic clones throughout central Europe [19], as well as shifts of epidemic strains found within Germany [20].

The decline in the incidence of invasive MRSA infections reported here is smaller and occurred later than that suggested by other German surveillance systems. For example, in the laboratory-based ARS network the

Table 1

Demographic characteristics of patients with invasive meticillin-resistant *Staphylococcus aureus* infection in Germany by year of notification, 2010–2014 (n=20,679)

Characteristics	Total	2010	2011	2012	2013	2014	P-value
N	20,679	3,754	4,227	4,485	4,372	3,841	–
Female n (%)	7,595 (37)	1,392 (37)	1,573 (37)	1,608 (36)	1,668 (38)	1,354 (35)	0.05
Median age in years (IQR)	74 (64, 80)	73 (65, 80)	73 (64, 80)	73 (64, 80)	74 (64, 80)	74 (64, 80)	0.47
Age group in years, n (%)							
<1	67 (0)	10 (0)	14 (0)	12 (0)	22 (1)	9 (0)	0.23
1 to 49	1,392 (7)	245 (7)	285 (7)	304 (7)	279 (6)	279 (7)	
50 to 59	2,159 (10)	400 (11)	458 (11)	485 (11)	445 (10)	371 (10)	
60 to 69	3,877 (19)	731 (19)	788 (19)	803 (18)	809 (19)	748 (19)	
70 to 79	7,508 (36)	1,321 (35)	1,554 (37)	1,641 (37)	1,569 (36)	1,423 (37)	
≥80	5,673 (27)	1,047 (28)	1,127 (27)	1,242 (28)	1,247 (29)	1,010 (26)	
Federal state of residence, n (%)							
Baden-Württemberg	1,234 (6)	292 (8)	248 (6)	253 (6)	255 (6)	186 (5)	<0.001
Bavaria	1,730 (8)	378 (10)	385 (9)	358 (8)	356 (8)	253 (7)	
Berlin	1,486 (7)	285 (8)	304 (7)	306 (7)	321 (7)	270 (7)	
Brandenburg	772 (4)	152 (4)	173 (4)	139 (3)	153 (4)	155 (4)	
Bremen	101 (0)	22 (1)	22 (1)	24 (1)	15 (0)	18 (0)	
Hamburg	214 (1)	0 (0)	57 (1)	26 (1)	67 (2)	64 (2)	
Hesse	1,274 (6)	302 (8)	266 (6)	271 (6)	257 (6)	178 (5)	
Mecklenburg-West Pomerania	653 (3)	97 (3)	134 (3)	143 (3)	145 (3)	134 (3)	
Lower Saxony	2,655 (13)	514 (14)	571 (14)	498 (11)	531 (12)	541 (14)	
North Rhine-Westphalia	6,123 (30)	944 (25)	1,160 (27)	1,457 (33)	1,354 (31)	1,208 (31)	
Rhineland-Palatinate	664 (3)	154 (4)	153 (4)	156 (3)	110 (3)	91 (2)	
Saarland	189 (1)	0 (0)	28 (1)	58 (1)	54 (1)	49 (1)	
Saxony	1,359 (7)	202 (5)	290 (7)	296 (7)	295 (7)	276 (7)	
Saxony-Anhalt	849 (4)	157 (4)	164 (4)	179 (4)	182 (4)	167 (4)	
Schleswig-Holstein	824 (4)	144 (4)	153 (4)	213 (5)	177 (4)	137 (4)	
Thuringia	547 (3)	111 (3)	119 (3)	105 (2)	98 (2)	114 (3)	
Type of area, n (%)							
Rural	12,649 (61)	2,278 (61)	2,596 (61)	2,715 (61)	2,723 (62)	2,337 (61)	<0.001
Urban	7,386 (36)	1,310 (35)	1,506 (36)	1,604 (36)	1,560 (36)	1,406 (37)	
Undefined	644 (3)	166 (4)	125 (3)	166 (4)	89 (2)	98 (3)	
Place of possible exposure, n (%)							
Other federal state than state of notification	275 (1)	39 (1)	55 (1)	64 (1)	55 (1)	62 (2)	0.26
Outside of Germany	40 (0)	4 (0)	5 (0)	11 (0)	10 (0)	10 (0)	0.34

IQR: interquartile range.

Only notifications marked as fulfilling the reference definition are included. Missing data were less than 0.1%, except for the exposure place, where the exact number could not be identified due to technical reasons.

percentage of oxacillin resistance in blood culture collected from inpatients declined from a peak of 24% (95% CI: 22.5–27.0) in 2010 to 18.4% (95% CI: 16.5–20.3) in 2011 [7] and is currently at 13% (www.ars.rki.de). The EARS-net reported a decline in the proportion of MRSA among *S. aureus* isolates for Germany from 20.9% in 2010 to 12.8% in 2013 [1], the triennial survey by the Paul Ehrlich Institute found a decline from 30.3% in 2007 to 16.7% in 2010 [21] and data from the hospital infections surveillance system (KISS) suggest a decline from 33% in 2007 to 27% in 2012 among nosocomial *S. aureus* infections [6]. This may in part be explained by the different indicators used and the possible non-representativeness of these voluntary systems, but more probably is due to the underreporting in the national reporting system in the first years. Thus a definite conclusion concerning the start of the decline cannot be made.

Despite the decrease in 2014, the incidence of 4.8 invasive MRSA infections per 100,000 persons in Germany is still higher than that in some neighbouring countries, such as Denmark (1 case of MRSA bacteraemia per 100,000 in 2014) [22], western Sweden (one case of community onset MRSA blood stream infection between 2004 and 2008 for a catchment population of 256,000) [23] and England, where, after intensification of control mechanisms, a recent decline was reported

Table 2

Clinical characteristics of patients with invasive meticillin-resistant *Staphylococcus aureus* infection in Germany by year of notification, 2010–2014 (n=20,679)

Characteristics	Total	2010	2011	2012	2013	2014	P-value
N	20,679	3,754	4,227	4,485	4,372	3,841	–
Type of specimen for diagnosis, n (%)							
Blood	19,318 (93)	3,587 (96)	3,837 (91)	4,156 (93)	4,126 (94)	3,612 (94)	<0.001
CSF	117 (1)	24 (0)	13 (0)	37 (1)	25 (1)	18 (0)	
CSF and blood	17 (0)	2 (0)	5 (0)	1 (0)	3 (0)	6 (0)	
Not indicated	1,227 (6)	141 (4)	372 (9)	291 (6)	218 (5)	205 (5)	
Clinical case definition fulfilled, n (%)							
Yes	18,775 (91)	3,343 (89)	3,855 (91)	4,133 (92)	3,967 (91)	3,477 (91)	<0.001
No	1,245 (6)	195 (5)	308 (7)	260 (6)	302 (7)	180 (5)	
Unknown	659 (3)	216 (6)	64 (2)	92 (2)	103 (2)	184 (5)	
Patients with available data on clinical symptoms, n (%)							
With data	18,268 (88)	3,329 (89)	3,609 (85)	3,978 (89)	3,890 (89)	3,462 (90)	<0.001
Clinical symptoms among those with available data (N=18,268), n (%)[a]							
Fever	13,697 (75)	2,444 (73)	2,739 (76)	3,036 (76)	2,876 (74)	2,602 (75)	0.02
Signs of meningitis, meningoencephalitis or meningomyelitis	1,813 (10)	44 (1)	493 (14)	494 (12)	457 (12)	325 (9)	<0.001
Pneumonia	3,494 (19)	588 (18)	681 (19)	778 (20)	760 (20)	687 (20)	0.15
Endocarditis	428 (2)	67 (2)	79 (2)	99 (2)	89 (2)	94 (3)	0.35
Lesion, skin abscess or ulcer	269 (1)	0 (0)	0 (0)	1 (0)	68 (2)	200 (6)	<0.001
Screening examination	304 (2)	0 (0)	0 (0)	0 (0)	64 (2)	240 (7)	<0.001
Sepsis	12,086 (66)	1,682 (51)	1,866 (52)	2,678 (67)	3,135 (81)	2,725 (79)	<0.001
Characteristics among patients with sepsis (N=12,086), n (%)[a]							
Central vein catheter or other invasive access	4,324 (36)	511 (30)	675 (36)	979 (37)	1,105 (35)	1,054 (39)	<0.001
Other foreign object associated infection	594 (5)	50 (3)	69 (4)	124 (5)	190 (6)	161 (6)	<0.001
MRSA infection of known focus	5,425 (45)	12 (1)	622 (33)	1,298 (48)	1,846 (59)	1,647 (58)	<0.001
Characteristics among MRSA infections of known focus (N=5,425), n (%)[a]							
Urinary tract	1,031 (19)	5 (42)	124 (20)	226 (17)	358 (19)	318 (19)	0.15
Abdomen (e.g. after operation)	267 (5)	1 (8)	35 (6)	75 (6)	90 (5)	66 (4)	0.20
Respiratory tract	1,777 (33)	1 (8)	208 (33)	438 (34)	587 (32)	534 (33)	0.31
Skin or soft tissue	2,291 (42)	4 (33)	265 (43)	576 (44)	781 (42)	665 (40)	0.27
Bones or joints	399 (7)	0 (0)	41 (7)	82 (6)	150 (8)	126 (8)	0.25
Other	596 (11)	2 (17)	67 (11)	140 (11)	217 (12)	170 (10)	0.67
Hospitalisation, n (%)							
Yes	18,423 (89)	3,281 (87)	3,753 (89)	4,065 (91)	3,897 (89)	3,427 (89)	<0.001
No	1,675 (8)	437 (12)	417 (10)	357 (8)	315 (7)	149 (4)	
Unknown	581 (3)	36 (1)	57 (1)	63 (1)	160 (4)	265(7)	
Date of onset of symptoms and of hospitalisation known, n (%)	11,273 (55)	1,774 (47)	2,163 (51)	2,490 (56)	2,510 (57)	2,336 (61)	<0.001
Among these, symptom onset while in hospital n (%)[b]	4,412 (39)	646 (36)	818 (38)	993 (40)	1,036 (41)	928 (40)	0.01
Vital status							
Vital status known n (%)	20,293 (98)	3,694 (98)	4,151 (98)	4,433 (99)	4,353 (100)	3,662 (95)	<0.001
Mortality among those with vital status known (N=20,293)							
All-cause mortality n (%)	1,973 (10)	320 (9)	366 (9)	437 (10)	396 (9)	454 (12)	<0.001
Case fatality rate n (%)[c]	1,580 (8)	319 (9)	354 (9)	359 (8)	293 (7)	255 (7)	<0.001
Time from symptom onset to death, median days (IQR)[d]	7 (3, 18)	9 (3, 20)	6 (3, 18)	8 (4, 21)	7 (3, 17)	6 (2, 15)	0.04

CSF: cerebrospinal fluid; IQR: interquartile range; MRSA: meticillin-resistant *Staphylococcus aureus*.

Only notifications marked as fulfilling the reference definition are included. Missing data were less than 1% or are as indicated.

[a] Several categories could apply simultaneously. Thus the total may tally to more than 100%.

[b] Onset > 2 days after hospitalisation and before or on discharge.

[c] MRSA infection identified as a cause of death.

[d] Based on patients with available data: n=187 in 2010, 252 in 2011, 295 in 2012, 289 in 2013, 335 in 2014.

in 2014 (with an incidence of 1.6 case of MRSA bacteraemia per 100,000 in that year) [24]. This indicates that still more needs to be done in Germany as well. Finally, a decline in invasive MRSA infections does not necessarily mean that other forms, such as livestock-associated and community-associated MRSA infections, are also declining. These forms are not properly captured by the surveillance system analysed here. However, data from the voluntary ARS system indicate declines in various forms of MRSA infections (https://ars.rki.de/).

A possible focus for further interventions should include the MRSA management in ambulatory settings and a more rigorous detection of outbreaks. Similar to data from various other countries [23,25], 61% of the patients with available hospitalisation and disease onset dates, had an onset before day three of hospitalisation, indicating that colonisation and infections may occur before hospitalisation possibly in the community. Furthermore, only 1% of cases were associated with outbreaks. While it is unclear, which proportion of MRSA infections is expected to be caused by outbreaks, we think that the notified number is a large underestimation, especially given the fact that only invasive infections are to be notified and detection of MRSA at other body sites is much more frequent. The increase in the number of reported outbreaks from 27 in 2012 to 38 in 2014 with a simultaneous decrease of the number of infected persons and an increase of colonised persons is however a promising sign, that more outbreaks are being detected and reported.

The mortality and case fatality rate of respectively 10% and 8% observed in this study were lower than those reported in the literature [26-28]. For example one study reported a case fatality rate of 22% for community-onset MRSA bacteraemia [28] and a multicentre prospective study in 13 European hospitals found a mortality for MRSA bloodstream infection of 36% [26]. We believe this to be due to the lack of a defined follow-up period in the German surveillance system. There are no strict rules for when the public health department should collect patient information including the treatment outcome. Therefore, the values presented here are likely to be underestimations.

The causes for the higher incidence among men are not clear, even though previously shown by other surveillance systems in Germany [4] and elsewhere [24]. In our data a difference according to sex becomes only apparent among older patients suggesting medical or behavioural factors in this age group as the key driver. More studies are however needed to better understand the underlying causes for this association. Similarly, studies are needed to investigate the causes for the higher incidence in the north of Germany.

The study has further limitations in addition to those already mentioned above. These include the absence of federal validation processes of the notification system, since communicable disease management is in the responsibility of the German federal states. A limitation is also the notification by patients' home addresses, which may not be the place of exposure. This may especially lead to an underestimation of the incidence in urban areas, if many patients from surrounding districts are treated in a nearby urban centre, but are notified for their home address. Finally, the number of software packages and versions available for the local public health office may result in different implementation of some variables, such as the clinical symptoms, which are difficult to understand retrospectively at the national level. Thus trends over time in some variables may be biased due to delayed updates of software or changes in the proportion of various software packages over time. Finally, the absence of a personal identifier does not allow identifying recurrent infections with certainty.

In summary, data from the national surveillance system corroborate previous reports that the incidence of MRSA infections in Germany may be declining. However, additional studies are needed to better understand its causes and to accelerate this still modest downward trend.

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Conflict of interest

None declared.

Authors' contributions

Design of the study: JH, MAS, SH, TE, JW. Analysis: JW, SH, HPB. Writing of the first draft: JW.

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Research article

Sub-Saharan African migrants living with HIV acquired after migration, France, ANRS PARCOURS study, 2012 to 2013

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We estimated the proportion of migrants from sub-Saharan Africa who acquired human immunodeficiency virus (HIV) while living in France. Life-event and clinical information was collected in 2012 and 2013 from a random sample of HIV-infected outpatients born in sub-Saharan Africa and living in the Paris region. We assumed HIV infection in France if at least one of the following was fulfilled: (i) HIV diagnosis at least 11 years after arrival in France, (ii) at least one negative HIV test in France, (iii) sexual debut after arrival in France. Otherwise, time of HIV infection was based on statistical modelling of first CD4+ T-cell count; infection in France was assumed if more than 50% (median scenario) or more than 95% (conservative scenario) of modelled infection times occurred after migration. We estimated that 49% of 898 HIV-infected adults born in sub-Saharan Africa (95% confidence interval (CI): 45–53) in the median and 35% (95% CI: 31–39) in the conservative scenario acquired HIV while living in France. This proportion was higher in men than women (44% (95% CI: 37–51) vs 30% (95% CI: 25–35); conservative scenario) and increased with length of stay in France. These high proportions highlight the need for improved HIV policies targeting migrants.

Introduction

In France, as in most countries in Western Europe, migrants from sub-Saharan Africa are disproportionally affected by the human immunodeficiency virus (HIV) epidemic [1,2]. In 2012, people born in sub-Saharan Africa accounted for 31% of new HIV diagnoses [3] and for 24% of the whole population of persons living with HIV (PLWHIV) in France [4], although they represented only ca 1% of the French general population [5]. Among people from sub-Saharan Africa, the number of new diagnoses has decreased in France since 2003, although incidence remains 29 times higher in men and 69 times higher in women compared with French-national heterosexuals [6].

Most people do not know where and when they acquired HIV. Among migrants, HIV acquisition has long been considered to predominantly occur before migration because of generalised HIV epidemics in sub-Saharan African countries [7]. However, evidence from various European countries in the past decade suggests that a substantial proportion of migrants from sub-Saharan Africa acquired HIV while they were living in Europe [8]. In the United Kingdom (UK), this proportion was recently estimated at 31% using a modelling approach based on CD4+ T-cell counts [9].

Such an estimate is not currently available for most European countries, although it is crucial to guide public health monitoring and allocation of resources for prevention. Indeed, if HIV is acquired after migration, resources should be allocated not only to improve timely HIV diagnosis but also to prevent the spread of HIV among migrants.

In this study, in order to guide HIV policies for migrants in France, we estimated the proportion of sub-Saharan migrants who acquired HIV infection after their arrival in France. This estimation was performed using life-event data and clinical data collected in the PARCOURS study, a large life-event survey [10] of people from sub-Saharan Africa living in the metropolitan area of Paris, the French area most affected by HIV [3] and with the

largest population of migrants from sub-Saharan Africa [5].

Methods

Study design

The PARCOURS study is a cross-sectional retrospective life-event history survey conducted between February 2012 and May 2013 among a random sample of sub-Saharan migrants receiving care for HIV at hospitals in the Paris metropolitan area. Of the 41 hospital services following HIV-infected patients in the Paris region, we selected the 37 services where at least 100 patients from sub-Saharan Africa were followed up. Within this sampling frame, hospital services were selected by stratified randomisation, the sampling probability of each HIV service being proportional to the size of the service's HIV caseload. A total of 27 services were chosen and 24 agreed to participate in the study. The caseload of these 24 services represented 72% of all sub-Saharan migrants followed for HIV in the Paris metropolitan area.

In each participating department, all outpatients born in a sub-Saharan African country, aged 18 to 59 years and diagnosed HIV-positive at least three months ago, were eligible. Physicians invited all eligible patients, except those with major cognitive or health impairments, to participate and collected their written consent. Professional interpreters were available on demand. Of a total of 1,829 eligible outpatients, 141 were excluded, and the participation rate among the remaining patients was 55%, resulting in a total of 926 participants. Among the participants, detailed information on migration history, socioeconomic conditions, sexual activity and health over the lifetime was collected anonymously through a standardised life-event questionnaire administered face-to-face by a trained professional interviewer independent from the clinic staff. The interview occurred in the clinic setting in a private room to ensure confidentiality. Each dimension of interest was documented for each year from birth until the time of data collection. Clinical and laboratory information were documented from medical records available in the health service where the survey was done. Basic data about non-participants were collected anonymously. There were no major differences between participants and non-participants in the demographic or clinical characteristics: the participation rate was higher among unemployed men compared with those working (60.1% vs 49.0%, p = 0.05), but did not vary by sex, age, or $CD4^+$ T-cell level. Participants received a voucher over EUR 15. The study was approved by the French National Commission for Data Protection and Liberties (CNIL, decision DR-2011–484). The complete survey protocol is registered on Clinicaltrials.gov (NCT02566148).

Information of interest

Information on year of HIV diagnosis was documented both from the participants' reports and medical records. Both sources provided concordant information (i.e. same year +/−1) in 81% (731/898) of the cases. In case of discordance, we retained the earliest date. Patient-reported years of arrival in France, negative HIV tests (if ever) and year of first intercourse were available in the life-event questionnaire. $CD4^+$ T-cell counts at the time of (i) HIV diagnosis, (ii) initiation of antiretroviral therapy (ART) and (iii) interview were extracted from medical records. We defined the first measurement of $CD4^+$ T-cell count as $CD4^+$ T-cell count at HIV diagnosis or, in case of missing information at diagnosis (n = 30), as first $CD4^+$ T-cell count available before initiation of ART.

Estimation of HIV acquisition after arrival in France

To assess whether HIV acquisition occurred before or after arrival in France, we used a combined method mixing life-event and $CD4^+$ T-cell data.

Based on life-event data, we considered that HIV infection had been acquired before arrival in France if HIV diagnosis occurred before living in France. In addition, we assumed that HIV infection had probably been acquired after arrival in France if at least one of the following life-event criteria were fulfilled: (i) HIV diagnosis at least 11 years after arrival in France [11,12], (ii) at least one negative HIV test in France, (iii) first sex after arrival in France. If none of these criteria was fulfilled, we estimated the duration from HIV infection to measurement of first $CD4^+$ T-cell count using statistical modelling of the decline in $CD4^+$ T-cell count based on a method previously described [13].

As we did not have information related to the seroconversion for PARCOURS respondents, we modelled the decline in $CD4^+$ T-cell using a cohort of West African seroconverters: the ANRS 1220 PRIMO-CI cohort of HIV-1 seroconverters in Abidjan, Côte d'Ivoire [13,14]. The PRIMO-CI cohort consisted of 351 blood donors (61% men; median age at HIV infection: 28.8 years; interquartile range (IQR): 25–34) followed from 1997 to 2011, with documented negative and first positive HIV antibody test dates and at least two $CD4^+$ T-cell counts available before commencement of ART or death. The decline in $CD4^+$ T-cell count (square root-transformed) over time was estimated using a linear mixed model with random intercept and slope, adjusted for individual $CD4^+$ T-cell count at first $CD4^+$ T-cell count measure (x_1) duration from estimated date of HIV seroconversion to first $CD4^+$ T-cell count measure (x_2) and age at HIV seroconversion (x_3).* With the fixed effects obtained from the fitted linear mixed model in this population of seroconverters, we first derived a formula to estimate the duration Δt from HIV seroconversion to any given $CD4^+$ T-cell count ($CD4_t$):

$$\Delta t = \frac{\left(\sqrt{CD4_t} - (12.108 + 0.02x_1 + 0.974x_2 - 0.002x_3)\right)}{-0.675 - 0.001x_1}$$

This formula was then used to estimate the duration from HIV seroconversion to first $CD4^+$ T-cell measurement before ART initiation for PARCOURS respondents.

For PARCOURS respondents, we simulated x_1, x_2 and x_3 using the observed multivariate distribution in the PRIMO-CI seroconverters cohort. For each PARCOURS respondent, we simulated 500 values of x_1, x_2 and x_3 from a multivariate normal distribution [15] in order to yield 500 extrapolated durations from seroconversion to first measurement of $CD4^+$ T-cell count. Then, we added three months to these durations to account for the duration between HIV infection and seroconversion.

The proportion of individuals having acquired HIV infection while living in France was estimated according to two scenarios. In the median scenario, the infection in each individual was assumed to have occurred after arrival in France if more than 50% of the simulated durations fell within the period of their stay in France, while the conservative scenario required 95% of durations within the period of staying in France.

Associations between HIV acquisition while living in France according to the conservative scenario and age at arrival in France, time lived in France before HIV diagnosis, region of birth in sub-Saharan Africa and time point of HIV diagnosis were analysed with bivariate and multivariate logistic regression models, for men and women separately. Multivariate models were adjusted for all variables mentioned above.

Data were weighted according to each individual's probability of inclusion in the survey, and the weights applied to all percentages. Analyses were conducted using STATA 13.0 (Stata Corp., College Station, Texas, United States).

Results

Life-event or $CD4^+$ T-cell data were missing for 28 individuals who were excluded from the analysis. Among the 898 respondents included, 550 were women and 348 were men. Median age at arrival in France was 28 years for women (IQR: 23–34) and 30 years for men (IQR: 25–37). Main countries of origin were Côte d'Ivoire (24%), Cameroon (20%), Democratic Republic of the Congo (13%), Mali (9%) and Congo (Brazzaville) (7%). The majority (81%) had at least a secondary educational level. At the time of interview, respondents had a median age of 43 years (IQR: 36–49; women: 40 years (IQR: 35–46); men: 47 years (IQR: 39–52)) and their median length of stay in France was 12 years (IQR: 7–20). At the time of HIV diagnosis, median time spent in France was three years (IQR: 1–9) and median $CD4^+$ T-cell count was 274/mm^3 (IQR: 129–430).

As shown in the Figure, of the 898 respondents included in the final study sample, 133 had been diagnosed with HIV before arrival in France and 765 had been diagnosed in France between 1983 and 2012. Overall 228 respondents were ascertained to have acquired HIV while living in France based on life-event criteria: 137 had been diagnosed at least 11 years after arrival in France, 63 had a history of negative HIV test in France, and 28 had their first sexual intercourse in France and had been infected neither perinatally nor through blood transfusion. Among the 537 who did not fulfil these criteria, based on first available $CD4^+$ T-cell count, 197 were ascertained by modelling to have acquired HIV after arrival in France according to the median scenario and 69 according to the conservative scenario (Figure). Overall, this led to estimates of 49% (95% CI: 45–53) and 35% (95% CI: 31–39) of sub-Saharan African migrants having acquired HIV while living in France, applying, respectively, the median and the conservative scenario.

This proportion who had acquired HIV after arrival in France was higher in men than in women (44% (95% CI: 37–51) vs 30% (95% CI: 25–35) in the conservative scenario) and among those who arrived in their youth (<25 years-old). It increased with the length of stay in France after migration. After adjustment for other variables, the proportion increased in the groups diagnosed most recently (odds ratio (OR) for 2008–12 vs 1996–2002 = 2.76 (95% CI: 0.74–10.29) for men and 2.50 (95% CI: 1.00–6.24) for women). No difference was found according to educational level and region of birth (Table).

Discussion

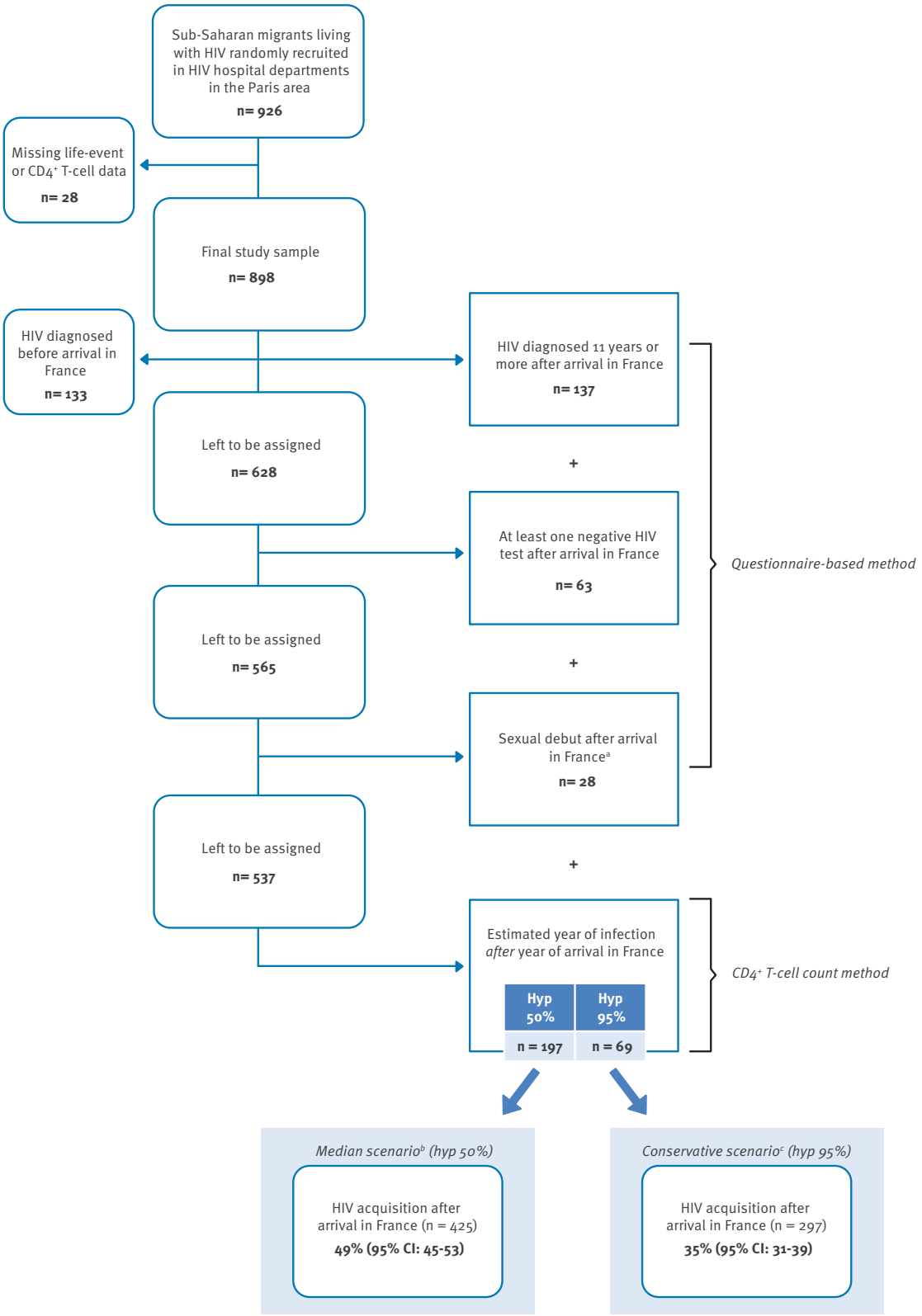
To our knowledge, this study is the first to provide an estimate of the proportion of sub-Saharan migrants having acquired HIV after arrival in France.

Our estimation was based on data from a random sample of HIV-positive hospital outpatients in the greater Paris metropolitan area. Since this region concentrates the major part of PLWHIV born in sub-Saharan Africa living in France (69% of women and 74% of men) [16] and HIV care in France is essentially provided at hospital [17], our results are likely to apply to the majority of sub-Saharan migrants followed for HIV in France.

Our results suggest that as much as one third to half of sub-Saharan African migrants followed for HIV care in France may have acquired HIV while living in France. French national HIV case surveillance data previously showed that 28% of sub-Saharan migrants newly HIV-diagnosed in France in 2003 to 2010 were infected with a B subtype, which is very rare in Africa, and are thus likely to have acquired HIV in Europe [18]. By comparison, when restricting our study to individuals diagnosed during the same period (since 2003, n = 508), we obtained an estimation of 35% (95% CI: 29–40) in the conservative scenario. This higher estimation is consistent with the fact that some migrants may have acquired a non-B HIV subtype in France, in particular within intra-African sexual networks. We found that men were more likely than women to have acquired HIV after migration. Such a result is consistent with the epidemiological pattern of the HIV

Figure

Assignment of HIV acquisition among Sub-Saharan African migrants living with HIV in the Paris metropolitan area, February 2012–May 2013 (n = 898)



CI: confidence interval; HIV: human immunodeficiency virus; hyp: hypothesis.

[a] Infected neither perinatally nor through blood transfusion.

[b] HIV acquisition while living in France if > 50% of the estimated years of infection fell within the period of staying in France.

[c] HIV acquisition while living in France if > 95% of the estimated years of infection fell within the period of staying in France.

Table

Estimated proportion of sub-Saharan African migrants living with HIV in Paris metropolitan area who acquired HIV after arrival in France, by sociodemographic characteristics and period of diagnosis, February 2012–May 2013 (n = 898)

	Men					Women				
				Univariate	Multivariate				Univariate	Multivariate
	n	Weighted[a] %	p value	OR (95% CI)	OR (95% CI)	n	Weighted[a] %	p value	OR (95% CI)	OR (95% CI)
Overall	348	43.9				550	30.0			
Age at arrival in France										
< 25 years	84	78.1	< 0.001	14.49 (6.84–30.68)	2.12 (0.65–6.90)	171	54.1	< 0.001	11.99 (5.30–27.13)	14.99 (4.14–54.25)
25–34 years	139	44.3		3.06 (1.47–6.39)	0.93 (0.31–2.84)	251	24.5		3.36 (1.65–6.82)	4.55 (1.72–12.03)
≥ 35 years	125	19.8		Reference	Reference	128	8.4		Reference	Reference
Time in France before diagnosis[b]										
0 to 2 years	137	10.3	< 0.001	Reference	Reference	254	5.4	< 0.001	Reference	Reference
3 to 5 years	45	19.3		2.25 (0.46–11.04)	2.12 (0.44–10.34)	93	23.4		5.90 (2.95–11.81)	6.56 (3.00–14.32)
6 to 9 years	39	54.0		11.08 (3.44–35.66)	14.48 (3.93–53.30)	67	52.5		21.42 (9.95–46.10)	26.44 (12.45–56.15)
10 years or more	106	93.5		117.38 (25.78–534.49)	166.23 (32.25–856.71)	95	86.0		110.28 (47.48–256.13)	219.87 (83.10–581.77)
Educational level										
None/primary	79	40.6	0.51	Reference	Reference	104	30.7	0.78	Reference	Reference
Secondary	160	41.1		1.02 (0.46–2.27)	2.30 (0.88–6.03)	334	30.8		1.05 (0.45–2.43)	1.23 (0.65–2.32)
Higher education	109	50.2		1.45 (0.67–3.11)	2.67 (0.74–9.64)	112	27.1		0.88 (0.28–2.83)	1.40 (0.60–3.27)
Region of birth in sub-Saharan Africa										
Western Africa	199	43.5	0.67	Reference	Reference	279	35.0	0.16	Reference	Reference
Central Africa	141	43.6		1.00 (0.54–1.85)	1.10 (0.48–2.48)	259	24.8		0.64 (0.38–1.08)	0.57 (0.32–1.01)
Eastern/ southern Africa	8	62.8		2.26 (0.32–15.98)	1.87 (0.05–76.93)	12	30.2		0.87 (0.18–4.23)	0.39 (0.08–1.97)
Year of diagnosis										
Earlier than 1996	49	51.7	0.61	1.73 (0.84–3.58)	1.12 (0.53–2.36)	67	40.3	0.14	1.58 (0.82–3.03)	0.27 (0.11–0.69)
1996–2002	89	38.3		Reference	Reference	185	29.9		Reference	Reference
2003–2007	105	45.9		1.40 (0.66–3.01)	2.88 (1.01–8.22)	179	31.7		1.08 (0.61–1.92)	2.39 (1.18–4.85)
2008–2012	105	43.0		1.24 (0.51–3.02)	2.76 (0.74–10.29)	119	22.2		0.67 (0.33–1.35)	2.50 (1.00–6.24)

CI: confidence interval; HIV: human immunodeficiency virus; OR: odds ratio.

[a] The Table presents the conservative scenario (hypothesis 95%): HIV acquisition while living in France if > 95% of the estimated years of infection fell within the period of staying in France. Data were weighted according to each individual's probability of inclusion in the survey (i.e. considering the probability of inclusion in the sample for each healthcare facility, the number of half-days of weekly consultations in each included facility and the individual study participation per half-day of included consultations).

[b] We excluded 21 men and 41 women from this multivariate analysis because data on $CD4^+$ T-cell count at diagnosis or before initiation of antiretroviral therapy were unknown.

epidemic in sub-Saharan Africa where women are infected at a younger age and to a higher proportion than men. Since HIV-infected men and women arrive approximately at the same age in France (median: 30 and 28 years, respectively, in our sample), women are more likely than men to be HIV-positive at the time they arrive in Europe. This also indicates that men might be at higher sexual risk in France after migration than women, as already suggested in UK and in France [19,20]. That the likelihood of acquiring HIV while living in France increases with time since arrival and with younger age at arrival further supports the validity of our estimation.

In the UK, 31% of black Africans born outside the UK and diagnosed HIV-positive between 2004 and 2010

were estimated to have acquired HIV while living in the UK [9]. Consistent figures were previously estimated based on life histories and $CD4^+$ T-cell count at presentation in healthcare centres between 2004 and 2006 [7]. Our results suggest that in France, the proportion of sub-Saharan African migrants living with HIV who acquired their infection after migration is even higher than in the UK. As in the UK, this proportion increased after 2000.

Rice et al. in the UK [9] estimated the time between HIV acquisition and diagnosis based only on modelling of the $CD4^+$ T-cell decline, whereas the major strength of our estimation lies in the combination of life-event and $CD4^+$ T-cell data. Although based on information given by the interviewees, histories of migratory path, HIV testing and sexual debut can be considered reliable since the life-event method greatly supports the recall process and the order of life events as shown previously [10,21]. Moreover, this mode of collection decreases the risk of desirability bias because the interviewer can compare the answers given for different periods and fields of the life. If inconsistencies are detected, they can check the reliability of the answer with the patient and correct it. To further strengthen this information, we checked the consistency between dates and circumstances of the negative HIV test in France and other life events such as pregnancies and sexual partnerships (data not shown). We assumed that patients acquired HIV only through sexual intercourse because less than 1% of sub-Saharan migrants living with HIV in France have been documented as IDU (data not shown, ANRS-VESPA study).

We used $CD4^+$ T-cell modelling to estimate the time between HIV acquisition and diagnosis only when the life-event criterion did not allow us to assign HIV acquisition before or after arrival in France. We modelled the natural decline in $CD4^+$ T-cell counts from a cohort of seroconverters in West Africa [14] to take into account possible genetic specificity of $CD4^+$ T-cell decline in HIV infection [22]. Since HIV disease progression does not differ across individuals from western and central Africa [23], estimates of the decline in $CD4^+$ T-cell count based on data from Côte d'Ivoire are likely to apply to our study population which consisted mostly of people originating from these two regions (96%). The model was also checked on data with life-event criterion available, and the results were consistent.

Our study has some limitations. Firstly, the natural history of HIV infection may be slightly different between African people living in Europe and those living in Africa: Pantazis et al. have shown that time between HIV infection and a certain level of $CD4^+$ T-cells is shorter in African people diagnosed for HIV in Europe than in African people diagnosed in sub-Saharan Africa [22]. In that case our modelling hypotheses would slightly underestimate the proportion of sub-Saharan African HIV-positive patients having acquired HIV after arrival in France.

Secondly, our estimation does not take into account HIV-positive migrants who are undiagnosed (estimated at ca one in four migrants with HIV [24]) or not in care. In France, migrants have free access to care after three months of residence, regardless of legal status. But it is still possible that some of them, in particular when recently infected and healthy, delayed their entry in care. This suggests that we may have underestimated the proportion of sub-Saharan African migrants living with HIV and having acquired HIV while living in France.

Thirdly, among PARCOURS participants, 1.3% were infected with HIV-2. Among them, some were assigned, based on life-event data, as having acquired HIV before/after arrival, leaving only 0.9% to whom we applied the slope of $CD4^+$ T-cell counts modelled for HIV-1. It is possible that for these 0.9%, we over-estimated the HIV-2 acquisition in France because the decline of $CD4^+$ T-cells is slower in HIV-2 infection. However, considering this low proportion, this is unlikely to have affected our overall results.

Finally, our sample was not large enough to investigate HIV acquisition in France among men who have sex with men (MSM): only 5% (n = 18) of the male participants declared having had male partners in their lifetime. The estimated proportion of post-migration HIV acquisition in this group did not appear significantly different from non-MSM. Nevertheless migrant MSM may be at high risk due to higher stigma and should be targeted in HIV prevention policies.

Conclusion

Despite possible underestimation, we estimated high levels of HIV acquisition after migration, which undermine the predominant postulate of HIV as a mainly imported epidemic among African migrants in Europe. It seems important that other European countries attempt to quantify post-migration HIV acquisition among migrants [25]. These results are necessary to guide allocation of prevention resources as in most countries in Europe, few prevention resources are allocated to activities targeting migrants because it is assumed that they were infected before arrival. Our results for France emphasise the need for a better understanding of sexual and preventive behaviour after migration to address the unmet preventive needs in the population born in sub-Saharan Africa and to design tailored public health policies in France.

*Erratum

This sentence was erroneously published as "The decline in CD4+ T-cell count (square root-transformed) over time was estimated using a linear mixed model with random intercept and slope, adjusted for individual CD4+ T-cell count at first CD4+ T-cell count measure (x1) duration from estimated date of HIV seroconversion to first CD4+ T-cell count measure (x1) and age at HIV seroconversion (x1)." The variables were corrected on 20 November 2015. We apologise for this mistake.

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Conflict of interest

None declared.

Authors' contributions

ADL, RDS, FL, NB and NL designed the research and organised the data collection, JP, AR and AG prepared the data, VS conceived and designed the CD4-count based modelling approach, JP, AR, AG and ADL analysed the data, ADL and JP drafted the manuscript and ADL, RDS, FL, VS, HP, NB, NL critically revised the manuscript for important intellectual content.

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ECDC publishes 2014 surveillance data on antimicrobial resistance and antimicrobial consumption in Europe

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In relation to the 8th European Antibiotic Awareness Day on 18 November, the European Centre for Disease Prevention and Control (ECDC) has published the annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) [1]. On the same occasion, an update with 2014 data of the EARS-Net interactive database on antimicrobial resistance [2] and the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) interactive database on antimicrobial consumption [3] was released, on the ECDC website.

The data on antimicrobial resistance showed that the percentages of *Klebsiella pneumoniae* isolates resistant to fluoroquinolones, third-generation cephalosporins and aminoglycosides, as well as combined resistance to all three antibiotic groups increased significantly at European Union (EU)/European Economic Area (EEA) level over the last four years. A significant increase was also observed for carbapenem resistance in *K. pneumoniae*.

For *Escherichia coli,* resistance to third-generation cephalosporins and combined resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides increased significantly at EU/EEA level. The increase in combined resistance, and the increase in resistance to last line groups of antimicrobials such as the carbapenems, is a serious cause for concern and a threat to patient safety in Europe.

Data on antimicrobial consumption in 2014 show that the overall consumption of antimicrobials in the community in the EU/EEA was 21.6 defined daily doses (DDD) per 1,000 inhabitants and per day. The large intercountry variation in antibiotic consumption observed in previous years remained. When antibiotic consumption was expressed in terms of number of packages (a better estimate for prescriptions) per 1,000 inhabitants and per day, five countries (Denmark, Luxembourg, Slovenia, Spain and Sweden) showed a significant decrease during 2010–2014.

During the same period, antibiotic consumption in the hospital sector (expressed in DDD per 1,000 inhabitants and per day) showed a significant increasing trend. A significant increase in the consumption of specific antibiotic groups, e.g. carbapenems, was also observed during this period at EU/EEA level, and in several countries. Although the vast majority of antibiotics is consumed in the community, i.e. outside hospitals, antibiotic consumption in hospitals is a major driver of the spread of multidrug-resistant bacteria responsible for healthcare-associated infections.

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