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## Costs and Outcomes of 1-year post-discharge care trajectories of patients admitted with infection due to antibiotic-resistant bacteria

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### SUMMARY

**Background:** The impact of antibiotic resistance (AMR) on initial hospital management has been extensively studied but its consequences after hospital discharge remain largely unknown. We aimed to analyze hospital care trajectories, cumulative length of hospital stays (c-LOS) and associated costs of care over a 1-year period after hospitalization with incident AMR infection.

**Method:** All incident bacterial infection-related hospitalizations occurring from January 1, 2015, to December 31, 2015 and recorded in the French national health data information system were extracted. Bacterial resistance ICD-10 codes determined six infection status. Inpatient and outpatient care consumption and associated costs were studied. The impact of resistance on c-LOS was estimated using a Poisson regression. A sequence analysis through optimal matching method was conducted to identify hospital trajectories along with an extrapolation.

**Finding:** Of the 73,244 patients selected, 15.9% had AMR infection, thus providing 58,286 incident AMR infections after extrapolation. c-LOS was significantly longer for infections with resistant bacteria, reaching 20.4 days and 2.9 additional days IC95%[2.6; 3.2] for skin and soft tissue infections. An estimated 29,793 (51.1%) patients had hospital readmission within the following year, for a total cost of €675 million. Five post-discharge trajectories were identified: Post-hospitalization mainly at home (68.4% of patients); Transition to home from rehabilitation care (12.3%); Early death (<3 months) (9.7%); Late death (7.4%), and Long-term hospitalization (2.2%).

**Interpretation:** AMR has an impact on patients' c-LOS stay beyond the initial hospitalization. Half of patients hospitalized due to AMR are readmitted to hospital within the ensuing year, along five different trajectories.

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### Introduction

Antimicrobial resistance (AMR) poses a major threat to public health.<sup>1,2</sup> Resistant infections worsen vulnerable patient conditions<sup>3</sup> and may threaten the ability to perform common medical procedures requiring antibiotics such as surgical intervention.<sup>4</sup> AMR results in higher mortality,<sup>5,6</sup> longer hospital stays, and

higher medical resource consumption.<sup>7</sup> With an increasing incidence<sup>8</sup>, health burden from AMR in Europe was estimated in 2015 at 670,000 infections and 33,000 attributable deaths.<sup>6</sup> In France, AMR caused 139,000 infections<sup>9</sup> and mortality was estimated to 5,543 deaths annually.<sup>6</sup>

Since 2011, AMR is recognized by the World Health Organization as a health priority requiring cross-disciplinary approach and robust information in order to prioritize and evaluate interventions. Economic evaluations are one of the tools for prioritizing healthcare policies.<sup>10</sup> Indeed, AMR causes substantial cost burden for the society. For example, from a third-party payer per-

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spective included federal and private insurance, estimated costs of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) ranged from \$478 million to \$2.2 billion in the US (2011).<sup>11</sup> Overall, in 2015, hospital costs associated with AMR infection was estimated to €290 million in France<sup>12</sup> from the public health insurance viewpoint. By 2050, the potential cost of AMR could reduce the gross domestic product by 2% to 3.5% worldwide, for an overall cost of \$100 trillion.<sup>13</sup> Although an abundant scientific literature allows to estimate the epidemiological and economic burden of AMR during the index hospitalization,<sup>14,15</sup> corresponding data related to post-discharge care remain largely unknown. Indeed, few studies analyze post-hospitalization clinical pathways and only for some specific infections. For example, mortality and readmission has been compared between patients with initial MRSA and methicillin-sensitive *S. aureus* (MSSA) bacteremia with a follow-up of five years and results show no difference in infection-related readmission;<sup>16</sup> likewise, healthcare-associated MRSA infections have been associated with a \$16,000 increased inpatient cost over the 1-year post-discharge period compared to patients without MRSA.<sup>17</sup>

The Public health impact of bacterial resistance to antibiotics (PhiBRA)<sup>18</sup> program aims to provide an overview of the burden of bacterial resistance to antibiotics in France. As part of the PhiBRA program, our objective was to provide a comprehensive description of the different hospital care trajectories, including cumulative hospital days and costs of care of patients over the year following hospital discharge from hospitalization with infection due to antibiotic-resistant bacteria. Therefore, we used the national health data system (SNDS: *système national des données de santé*), which contains individual data used for charging and reimbursing ambulatory care consumption and hospitalization.<sup>19</sup>

## Material and Methods

### Data Sources

The SNDS database contains information on each health spending reimbursement, as well as demographic characteristics (such as sex, age, vital status, etc.)<sup>19</sup> for each patient (information available in the SNDS database are described in the supplementary material, Appendix 1).

Data extraction and analysis were approved by the French Data Protection Agency (CNIL, approval DE-2016–176).

### Study Population

The study population included all patients aged over 18 years having a first incident hospitalization ( $\geq 1$  day), referred to as the index hospital stay, in acute-care facilities (MSO) for an acute infection related to *Staphylococcus*, *Enterobacteriaceae*, *Streptococcus*, and other Gram-negative bacteria in primary diagnosis (PD) identified in 2015, and alive at hospital discharge. To select for incident hospitalization, we excluded those patients having a hospital admission with the same infection in PD, related diagnosis (RD) or significant associated diagnoses (SAD) recorded in the preceding year.

As reported in a previous study,<sup>9</sup> numerous hospitalizations with an infection PD are not associated with an identified infecting microorganism code. Two groups were then defined, one with at least one microorganism recorded and a second without. From the group with defined microorganisms (referred to as the selected population), stays with at least one ICD-10 code filled for AMR in SAD were considered as *resistant* and those without such code as *susceptible*. The list of ICD-10 codes used has been described in a previous article (for more details, please refer to Opatowski

et al. (2019; Supplementary Material:Table 1).<sup>9</sup> In case of multiple infections or multiple organisms or resistance status, the infection cannot be properly identified since the database does not allow linking an infection with the responsible bacteria or bacteria with their resistance status, except for some specific combined codes (such as methicillin-resistant *S. aureus*, MRSA). To reduce the number of stays excluded because of unrecorded microorganism/resistance pair, a previously elaborated algorithm<sup>9</sup> was used to retain some of such hospitalizations in the selected population. In the situation where an infection has several identified organisms, resistance was attributed to the most relevant bacteria identified: methicillin resistance was assigned to *S. aureus*, extended spectrum  $\beta$ -lactamases (ESBL) resistance to *Enterobacteriaceae* or other Gram-negative bacteria and vancomycin resistance to *Enterococcus*. If attribution was not possible, patients with multiple microorganisms were excluded from the sample. In addition, non-concordant microorganism–resistance pairs were recoded to the nearest most relevant (e.g. penicillin-resistant *Enterobacteriaceae* as ESBL, and vancomycin-resistant *Streptococcus* as *Enterococcus*). Finally, when assignment to a given microorganism was not possible because of several resistance codes or impossible recoding, AMR status was retained, but resistance was classified as ‘unknown’.

To analyze patients' trajectories during the one-year follow-up after the index hospitalization, the patients' status was classified considering subsequent hospitalizations as follows: stay in an acute-care facility with (IMSO) or without infection (MSO) coded in PD, rehabilitation care stay (RHC), or in hospital at home (HAH); when a patient was in none of these facilities and still alive, he was considered at home (HOM); all-cause mortality was also taken into account thus defining a state of death (DEA). For outpatients, we collected all reimbursed services and medical products costs.

### Variables and statistical analysis

Baseline characteristics of the selected population, stratified on resistance status, were described with sex, age, Charlson comorbidity index,<sup>20</sup> and number of all-cause hospitalization in the previous year, not due to the same infection. Six infections sites were retained, including: (1) Urinary and genital tract, (2) Skin and soft tissue, (3) Lower respiratory tract, (4) Gastrointestinal and abdominal, (5) Bone, joint and Device-Associated, (6) Heart and mediastinum.<sup>9</sup>

Follow-up data of the selected population were described with mean ( $\pm$  standard deviation, SD) cumulative lengths of stay (c-LOS), including patient admission in day-care center ( $< 1$  day) considered as full day hospitalization; when necessary, length of stay was censored at 1 year from the day of discharge from the index hospitalization.

Two analyses were performed on the follow-up. In the first analysis, the whole selected population was used. The c-LOS in days during the follow-up was studied for all and each distinct sector (MSO, IMSO, RHC, and HAH). Multivariate Poisson regressions were used to estimate and quantify the impact of AMR for each c-LOS.<sup>21,22</sup> Baseline characteristics described in Table 1 were included in the regression. Given that the time spent in care sectors are not independent of each other, we also included in the regression analysis for each sector the c-LOS in the other sectors. Excess lengths associated with AMR infection were calculated by comparing the predicted means of the c-LOS of interest between patients having or not AMR infection at the index hospitalization.

To analyze patients' trajectories, the second analysis concerned only patients having an index hospitalization for an infection with AMR and hospitalized for any cause within the following year (excluding day-care center). Each day of follow-up was assigned to one of the sector (MSO, IMSO, RHC, HAH, HOM and DEA), which allowed to generate a sequence of care with a daily granularity for

**Table 1**  
General characteristics of patients with or without AMR infection at the index hospitalization.

Baseline characteristics	without AMR (n = 61,564)	with AMR (n = 11,680)	with AMR and rehospitalized <sup>1</sup> (n = 6,419)
Male sex, No. (%)	28,410 (46.1)	5,575 (47.7)	3,223 (50.2)
Age, years, No. (%)			
18–35	7,606 (12.4)	1,190 (10.2)	344 (5.4)
36–55	10,764 (17.5)	1,801 (15.4)	781 (12.2)
56–65	8,273 (13.4)	1,631 (14.0)	909 (14.2)
66–75	10,458 (17.0)	2,154 (18.4)	1,315 (20.5)
≥76	24,463 (39.7)	4,904 (41.8)	3,070 (47.8)
Charlson index, mean (SD)	0.9 (1.5)	1.0 (1.6)	1.3 (1.8)
0–No. (%)	36,741 (59.7)	6,698 (57.3)	3,012 (46.9)
1–2	18,188 (29.5)	3,481 (29.8)	2,246 (35.0)
3–4	4,239 (6.9)	977 (8.4)	729 (11.4)
≥5	2,396 (3.9)	524 (4.5)	432 (6.7)
Number of all-cause hospitalization in the previous year, No. (%)			
0	38,959 (63.3)	6,305 (54.0)	2,661 (41.5)
1	10,905 (17.7)	2,246 (19.2)	1,317 (20.5)
2 or 3	8,172 (13.3)	2,009 (17.2)	1,486 (23.2)
≥4	3,528 (5.7)	1,120 (9.6)	955 (14.9)
Site of infection, No (%)			
Urinary and genital tract	34,225 (55.6)	6,877 (58.9)	3,667 (57.1)
Bone, joint and device-associated	4,675 (7.6)	1,353 (11.6)	905 (14.1)
Gastrointestinal and abdominal	7,261 (11.8)	1,182 (10.1)	508 (7.9)
Skin and soft tissue	4,981 (8.1)	1,030 (8.8)	453 (7.1)
Lower respiratory tract	8,456 (13.7)	846 (7.2)	553 (8.6)
Heart and mediastinum	1,966 (3.2)	392 (3.4)	334 (5.2)
Pathogens, No. (%)			
<i>E. coli</i>	31,757 (51.6)	6,358 (54.4)	3,157 (49.2)
<i>S. aureus</i>	5,454 (8.9)	2,086 (17.9)	1,253 (19.5)
<i>K. pneumoniae</i>	2,585 (4.2)	864 (7.4)	569 (8.9)
Others	21,768 (35.4)	2,372 (20.3)	1,440 (22.4)
Hospital status, No. (%) of public	49,877 (81.0)	9,453 (80.9)	5,300 (82.6)
Cost of stay, mean (SD), in €	3,473 (3,320)	4,461 (3,936)	5,147 (4,512)
Length of stay, mean(SD), in days	7.5 (6.8)	8.7 (8.5)	10.4 (9.7)

AMR: antimicrobial resistance; SD standard deviation;

<sup>1</sup> at least one time during the follow-up, excluding day care center.

each patient, subsequently described by a chronogram.<sup>23</sup> Using the optimal matching method<sup>24,25</sup> followed by a clustering method allows obtaining care sequences pattern. Due to the lack of recorded microorganisms for some stays, an extrapolation was performed assuming that these stays were comparable to the selected population with microbiologically documented infection regarding sex, age and infection sites.<sup>9</sup> Thus AMR distribution and repartition of care sequence patterns was extrapolated to the number of patients in each care trajectory groups as well as patient characteristics.<sup>9</sup>

Data management was performed using SAS Enterprise Guide v7.13 and sequence analyses using Rstudio 1.1.456 with package TramineR. Statistical analyses were performed with SAS Enterprise Guide v7.13 and STATA/SE 15.0.

## Results

In 2015, of the 584,238 hospitalizations with any of the selected infections in PD, 43,902 (7.5%) were not incident infections, 86,214 (14.8%) were related to several infections or microorganisms and 31,162 (5.3%) had died at discharge (Fig. 1). Of the 422,960 remaining hospitalizations related to an incident infection, only 17% (N = 73,244) had information about the associated microorganism and were retained in the selected population. Among these, 16% (N = 11,680) were hospitalized for AMR infection, of which 55% (N = 6,419) were hospitalized at least once during the one-year follow-up.

### Baseline characteristics

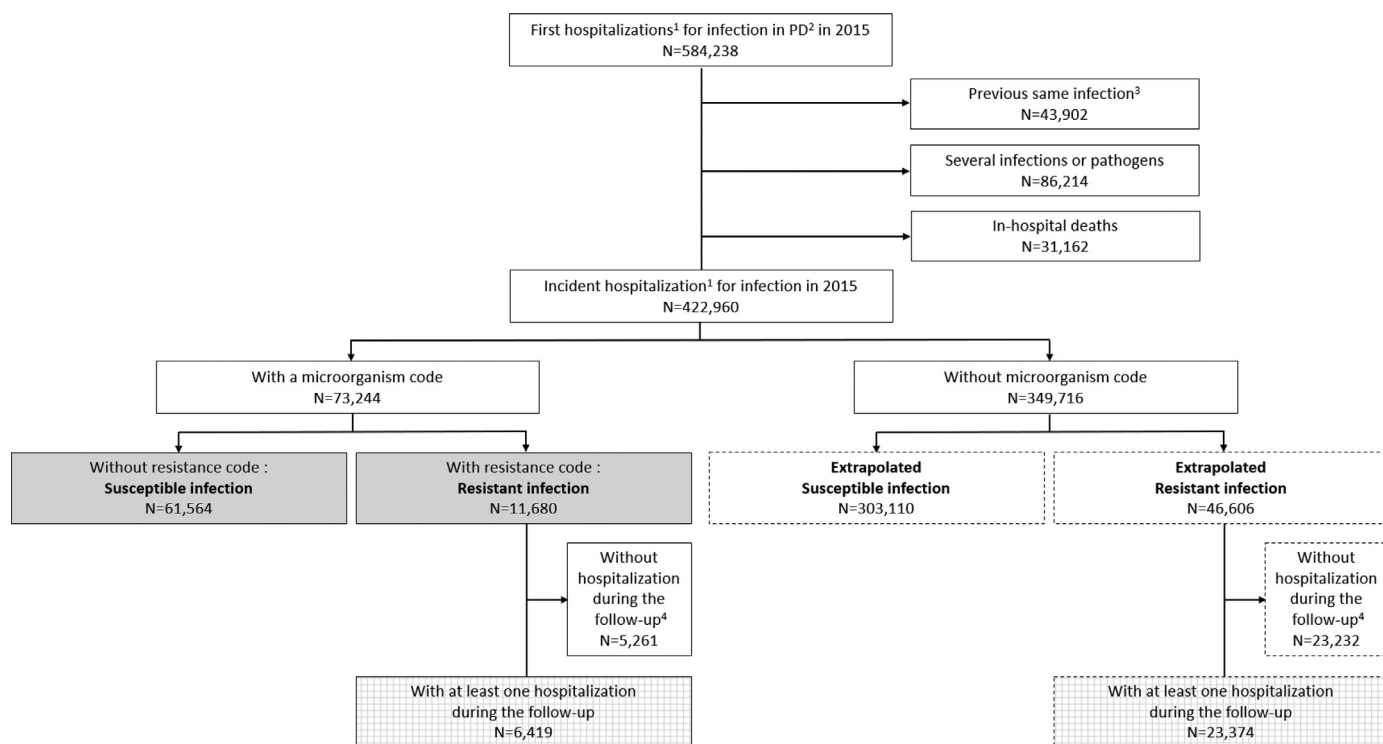
Table 1 shows the baseline characteristics at discharge from the index hospitalization of the patients with defined infection due to AMR bacteria or to an antibiotic-susceptible one retained in the se-

lected population. Patients in the two groups had similar age distribution, sex ratio and Charlson comorbidity index. Patients with AMR infection differed from their counterparts in terms of number of all-cause hospitalization in the previous year, with more history of hospitalization (46% vs. 37%) and also differed by infection site, with fewer respiratory tract infections (7.2% vs. 13.7%) and more bone, joint and device-associated infections (11.6% vs. 7.6%). Additionally, patients with antibiotic-resistant infections had more *Staphylococcus aureus*, *Klebsiella* and *E. coli*. Costs of the index hospitalization in the acute care sector of patients with AMR were higher compared to those without AMR (€4,461 vs. €3,473). Indeed, AMR infection was associated with a longer mean length of stay (8.7 vs. 7.5 days).

Patients having AMR infection and rehospitalized during the follow-up were older than the overall patients group with resistant infection, with almost half of them over 75 years old; a greater proportion of this subgroup had a history of at least one previous hospitalization or a Charlson comorbidity index above 3 (18.1% vs. 12.9%). Lastly, their index hospitalization was longer (10.4 days) and incurred higher cost (€5,147).

### Impact of antimicrobial resistance on cumulative length of hospitalization during the follow-up

From multivariate Poisson regression model, estimated mean of c-LOS after AMR infection, associated 95% confidence interval (95% CI) and corresponding excess days compared to susceptible ones are shown in Table 2. For all sectors, mean of c-LOS after AMR infection was greater than 14 days for all infections and reached 34.0 days (95% CI [33.7; 34.4]) for bone, joint and device-associated infections.

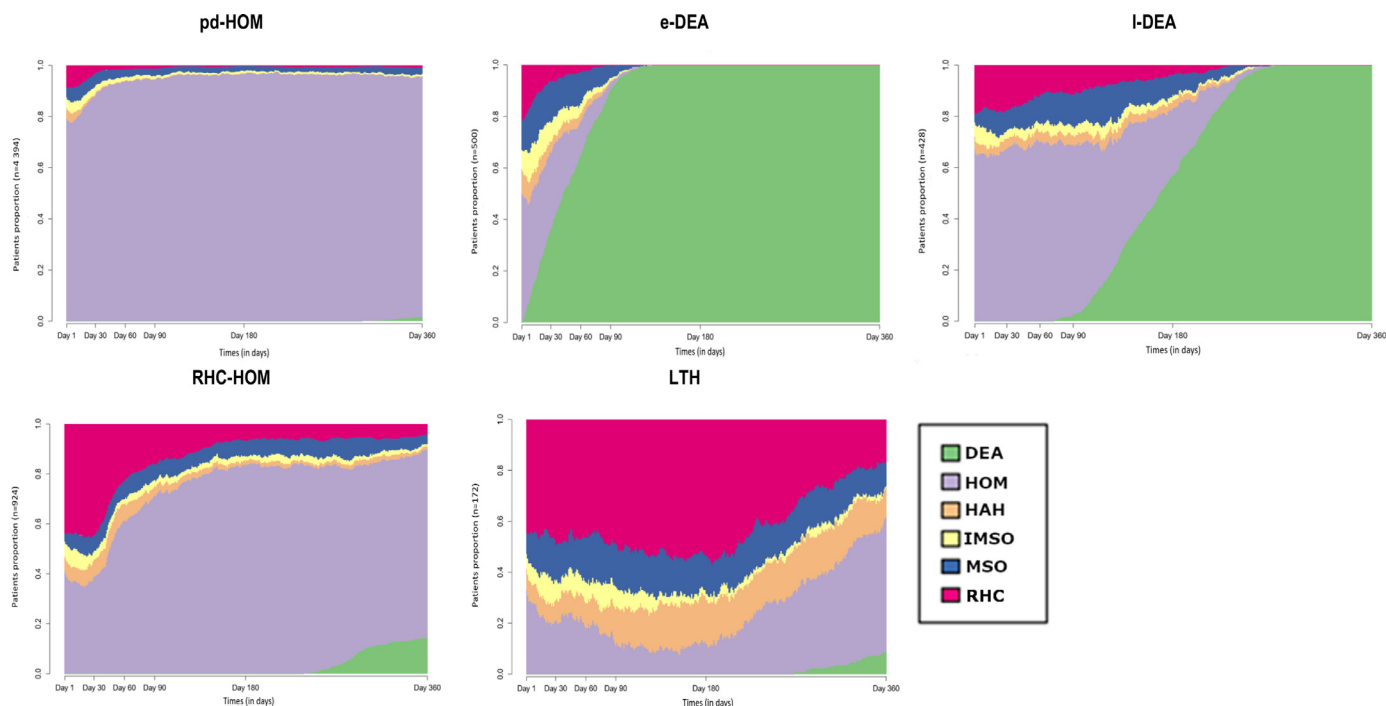


**Fig. 1.** Flowchart of the selected and extrapolated populations of the study, from the French national health insurance databases  
 Legend: 1 Hospitalization greater than 1 day; 2 primary diagnosis; 3 in the 12-months before; in grey : sample used for the study of the cumulative length of hospitalization; with square : restricted sample for the sequence analysis; dotted lines indicated extrapolated sample; 4 Are excluded even the patients without hospitalization but with day-care center admission

**Table 2**

Estimated mean [95% confidence interval] of cumulated length of hospital stay (c-LOS) after AMR infection (in days) and corresponding excess days compared to susceptible infection, for all and specific sectors and each location of infection: multivariate Poisson regression model. AMR: antimicrobial resistance; HAH: hospital at home; IMSO: stay in MSO for infection; MSO: medicine surgery and obstetrics; RHC: rehabilitation care.

(No. AMR/susceptible) (11,680/61,564)	All sectors	MSO	IMSO	RHC	HAH
<b>Urinary and genital tract</b>					
Mean c-LOS in days	15.6 [15.5; 15.6]	6.5 [6.4; 6.6]	2.1 [2.1; 2.3]	5.6 [5.6; 5.7]	1.5 [1.5; 1.5]
Excess days					
in days	1.3 [1.2; 1.4]	0.1 [0.1; 0.2]	0.8 [0.8; 0.9]	-0.7 [-0.7; -0.6]	0.6 [0.6; 0.6]
in %	9.3 [8.6; 10.0]	1.6 [0.5; 2.3]	61.5 [58.5; 64.6]	-10.8 [-11.7; -9.9]	68.4 [64.5; 72.2]
<b>Bone joint and material</b>					
Mean c-LOS in days	34.0 [33.7; 34.4]	4.5 [4.4; 4.6]	3.5 [3.4; 3.6]	20.4 [20.2; 20.7]	3.6 [3.4; 3.7]
Excess days					
in days	1.9 [1.6; 2.2]	0.1 [-0.0; 0.2]	0.5 [0.4; 0.6]	-0.5 [-0.8; -0.3]	1.5 [1.4; 1.6]
in %	6.0 [5.0; 7.0]	1.4 [-0.9; 3.8]	15.8 [12.5; 19.1]	-2.4 [-3.6; -1.2]	70.1 [65.2; 75.2]
<b>Gastrointestinal and abdominal</b>					
Mean c-LOS in days	14.7 [14.5; 14.9]	5.7 [5.5; 5.8]	2.8 [2.7; 2.9]	4.2 [4.1; 4.4]	1.8 [1.7; 1.9]
Excess days					
in days	1.8 [1.5; 2.0]	-0.1 [-0.2; 0.1]	0.9 [0.8; 1.0]	-0.6 [-0.7; -0.4]	1.1 [1.0; 1.1]
in %	14.9 [12.8; 16.9]	-1.0 [-3.7; 1.8]	46.8 [40.8; 53.1]	-11.9 [-14.7; -8.9]	135.8 [123.3; 149.0]
<b>Skin and soft tissue</b>					
Mean c-LOS in days	20.4 [20.1; 20.7]	6.8 [6.6; 7.0]	3.0 [2.8; 3.1]	6.5 [6.3; 6.7]	3.6 [3.4; 3.7]
Excess days					
in days	2.9 [2.6; 3.2]	1.2 [1.0; 1.4]	0.7 [0.5; 0.8]	-0.6 [-0.8; 0.4]	0.8 [0.7; 0.9]
in %	16.5 [14.6; 18.5]	21.7 [18.4; 25.1]	28.7 [23.2; 34.4]	-9.1 [-11.7; 6.3]	30.1 [25.0; 35.5]
<b>Lower respiratory tract</b>					
Mean c-LOS in days	18.8 [18.6; 19.1]	6.7 [6.5; 6.8]	2.8 [2.7; 2.9]	6.8 [6.6; 6.9]	1.7 [1.6; 1.8]
Excess days					
in days	1.9 [1.7; 2.2]	-0.3 [-0.4; -0.1]	1.0 [0.9; 1.1]	0.0 [-0.1; 0.2]	0.8 [0.7; 0.9]
in %	14.5 [12.9; 16.2]	-3.4 [-6.0; -1.6]	52.3 [46.7; 58.1]	0.1 [-2.3; 2.5]	86.6 [78.4; 95.3]
<b>Heart and mediastinum</b>					
Mean c-LOS in days	27.5 [27.1; 27.9]	5.9 [5.8; 6.1]	4.5 [4.4; 4.7]	9.7 [9.5; 10.0]	2.8 [2.7; 2.9]
Excess days					
in days (p-value)	-2.5 [-2.9; -2.1]	-1.9 [-2.1; -1.8]	0.3 [0.1; 0.4]	-0.7 [-0.9; -0.3]	0.6 [0.5; 0.7]
in %	-7.2 [-8.6; -5.8]	-24.6 [-26.6; -22.6]	5.9 [2.0; 10.0]	-5.8 [-8.2; -3.2]	27.2 [22.2; 32.4]
<b>All infections</b>					
Mean c-LOS in days	18.4 [18.4; 18.5]	6.2 [6.2; 6.3]	2.6 [2.6; 2.7]	7.2 [7.2; 7.3]	2.0 [2.0; 2.0]
Excess days					
in days (p-value)	1.3 [1.3; 1.4]	-0.0 [-0.1; 0.0]	0.7 [0.7; 0.8]	-0.6 [-0.6; -0.5]	0.8 [0.7; 0.8]
in %	7.8 [7.3; 8.3]	-0.5 [-1.3; 0.2]	39.8 [38.1; 41.6]	-7.3 [-7.9; -6.6]	62.7 [60.4; 65.0]



**Fig. 2.** Daily distribution of states of all patients with antimicrobial resistance infection and at least one rehospitalization during follow-up, by care sequence patterns (Chronogram).

Legend: DEA: death; e-DEA: Early death; HAH: hospital at home; HOM: at home; I-DEA: Late death; IMSO: stay in MSO for infection; LTH: Long-term hospitalization; MSO: medicine, surgery and obstetrics; pd-HOM: Post-discharge mainly at home; RHC: rehabilitation care; RHC-HOM: Transition to home from rehabilitation care. Note: This figure is composed of 5 chronograms for each of the 5 identified care-trajectories. On the x-axis, time is graduated from the discharge (at day 1) to 360 days after discharge. The y-axis corresponds to the proportion of patients (from 0 to 1). Each day, patients' proportion in different sectors can be visualized. For example, in e-DEA group, half of patients died before the 43rd day of follow-up, whereas "I-DEA" group is characterized by a cumulative mortality rate reaching 50% at day 16, i.e. 4 times later than e-DEA group.

The overall number of hospital days after infection with AMR or a susceptible organism differed significantly. AMR was associated with an increased c-LOS for bone, joint and device-associated infections (1.9 days [1.6; 2.2]), lower respiratory tract (1.9 days [1.7; 2.2]), and for skin and soft tissue infections with 2.9 days in excess [2.6; 3.2]. Heart and mediastinum infections were the only category associated with a decrease in the cumulative number of hospital days (-2.5 days [-2.9; -2.1]). Overall, AMR was associated with an increase of c-LOS in IMSO (0.7 days [0.7; 0.8]) and in HAH (0.8 days [0.7; 0.8]) but also with a decrease c-LOS in RHC (-0.6 days [-0.6; -0.5]).

**Care trajectories**

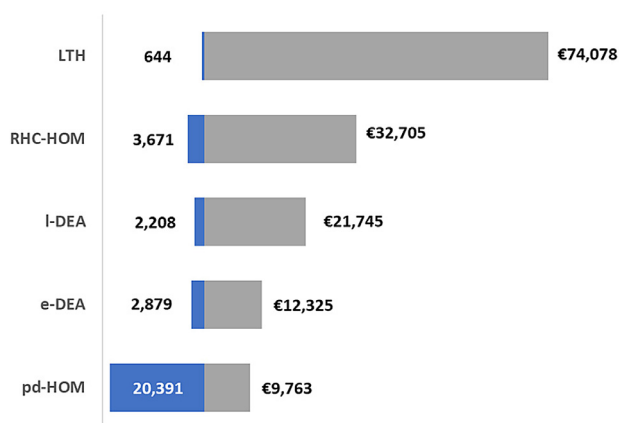
These analyses first focused on the 6,419 patients having had an index hospitalization with AMR infection and who were readmitted (excluding day-care center) during the 1-year follow-up (Fig. 1). The characteristics for each pattern defined by the sequence analysis were secondarily extrapolated to the whole population, thus adding 23,374 (6.6%) hospitalizations for incident infections with a presumed resistant organism, but without a specified microorganism (Fig. 1). The extrapolation led to a total of 58,286 patients with incident resistant infection in 2015, of whom 29,793 (51.1%) were readmitted to hospital in the following year.

Among the 6,419 patients with AMR infection at index hospitalization, 30.4% were directly hospitalized during the first day of follow-up and the readmission rate peaked on the 7th day at 32.8% (Appendix 5). The most solicited hospital sector in the beginning of the follow-up was RHC (around 15% at day 1 and 7) but the proportion of patients staying in RHC gradually declined until the end of the follow-up with 5.1%, 2.8% and 1.7% at day 90, 180 and 360 respectively. Overall, readmissions in the acute-care sector re-

mained below 15%; it was higher in the short-term with 8.7% and 12.5% at day 1 and 7 (4.0% and 7.0% for MSO without infections respectively and 4.7% and 5.5% for IMSO) and then decreased from 6.4% at day 90 to 3.1% at day 360 (including 4.6% and 2.5% respectively for MSO without infections and 1.8% and 0.6% for IMSO). The use of HAH was below 5% and decreased continually during the follow-up to 0.6%. Finally, mortality reached 7.2% and 11.6% respectively at days 90 and 180 and 17.9% at day 360.

From the selected population, five patterns of pathway trajectories during the post-discharge period were identified by sequence analysis (Appendix 2, 3 & 4, Fig. 2), and were designated as follows: (1) Post-discharge mainly at home (pd-HOM); (2) early ( $\leq 3$  months) death (e-DEA), (3) late death (I-DEA), (4) transition to home from RHC (RHC-HOM), (5) long-term hospitalization (LTH). The pd-HOM pattern was characterized by hospitalization concentrated at the beginning of follow-up with sporadic hospital stays throughout the year and a low mortality rate (1.7% at day 360). Mean time spent in home was 340 days in this group. For e-DEA pattern, 50% of patients in this group died before the 43rd day of follow-up, while for the I-DEA pattern, the median survival was reached at day 160. RHC-HOM included patients who experienced hospitalization in RHC during the first months of follow-up (49 days in average) with a transition to home. Finally, patients included in LTH pattern spent in average 275 days in hospital throughout the follow-up, with a mean duration of 151 days in RHC.

After extrapolation, patients' distribution among each pattern is apportioned as follows: 68.4%, 9.7%, 7.4%, 12.3% and 2.2% respectively in pd-HOM, e-DEA, I-DEA, RHC-HOM and LTH (Appendix 4). Compared to characteristics of the total population (N=29,793), gastrointestinal and abdominal infections were more common in pd-HOM (30.0% vs. 25.1%) whereas both e- and I-DEA patterns



**Fig. 3.** Mean cumulative post-discharge hospitalization cost per patient by trajectories – Patients with index hospitalization for infection with antimicrobial resistant bacteria and rehospitalized, after extrapolation (N = 29,793). The number of patients (blue portion) is shown on the left and corresponding costs in each care trajectory on the right of each bar.

had a higher proportion of lower respiratory tract infection (48.1% and 41.2% vs. 26.7% in the whole population) and of heart and mediastinum infections (10.4% and 7.3% vs. 5.6%). Both RHC-HOM and LTH patterns included a higher proportion of bone, joint and device-associated infections (14.1% and 18.3% vs. 5.8%) as well as heart and mediastinum infections (8.2% and 8.8% vs. 5.6%). Finally, a higher proportion of for skin and soft tissue infections was observed in LTH pattern (20.3% vs. 14.3%). In accordance with infection sites, pathogens more often involved in infections compared with the total population were *E. coli* for pd-HOM (42.9% vs. 39.1%), *Klebsiella* for e- and I-DEA (11.5% and 11.9% vs. 7.7%) and *S. aureus* for RHC-HOM and LTH (32.4% and 40.6% vs. 24.1%).

According to our extrapolation, over one year of follow-up, patients with AMR infection and at least one hospitalization had a total resource consumption, of €675 million, with the pd-HOM and RHC-HOM patterns accounting for the highest global costs of €346 million and €152 million respectively (Appendix 4). For all groups, mean hospital costs were 1.6 times higher than average ambulatory cost and this difference was up to 5.9 times higher for the e-DEA group. RHC-HOM and LTH patterns were the most expensive trajectories with the largest hospitalization costs per patient (respectively €32,705 and €74,078) for a means c-LOS of 91 days and 269 days (Fig. 3).

## Discussion

In this study, we provide a detailed description of care trajectories from an index hospitalization for infection with AMR bacteria, using a large nationwide cohort of patients with 1-year follow-up. We also report excess days for AMR infection in acute care facilities with admission for infections and hospital at home (Table 2). A major result is the documentation of a complex, long and expensive care trajectory for patients hospitalized for bone, joint and device-associated infections and lower respiratory tract infections with AMR (Table 2 and Supplementary Material: Appendix 4). Although these trajectories involve a limited number of patients, they incur a significant economic burden (Appendix 4).

Our findings are consistent with other studies focusing on post-discharge events. For example, we found that 60.1% of patients with resistant *S. aureus* required hospital transfer or readmission post-discharge (Table 1), which is comparable with the 65.4% rate reported for bloodstream infection with *S. aureus*.<sup>26</sup> An increased risk of readmission after AMR infections was also reported in other studies (Table 2).<sup>[17,27–29]</sup> However, none of these studies has doc-

umented as extensively as ours the trajectories of patients with resistant infection within the various healthcare facilities categories. This can help decision-makers to decide between different action modes and prevention across several hospital episodes.

An increase average length of hospitalization at home in all categories of infection for patients with resistant infection was found in our analyses (Table 2). This result may indicate a tendency to complete patient management by outpatient parenteral antibiotic therapy.<sup>30</sup> It also highlights the need to take a time horizon long enough and to consider all care sectors to capture the entirety of AMR consequences, as considering only the index hospitalization could underestimate the burden of AMR.

One of the strengths of the database analyzed (SNDS) is that it covers all hospital stays in France and all reimbursed care consumption. This allowed us to follow each patient for 1 year beyond the index hospital stay discharge. However, the primary objective of SNDS is the management of reimbursements. Therefore, important information from an epidemiological perspective may not be present. This is the case for microorganisms data, which led us to extrapolate this information from a selected population in order to describe the overall burden of each care trajectories for the whole population. Lack of microorganism identification in the infection could be explained by the database structure, since it is a financial database used as part of care reimbursements and does not always provide ICD-10th code for all bacteria. Second, microbiological investigations are not always performed upon infections due to the impracticality of collecting microbiological sample, or the use of a broad-spectrum antibiotic as first-line treatment. Our extrapolation method was validated in another study,<sup>9</sup> which has shown consistent results with other European surveillance data for AMR incidence in France. Furthermore, ICD-10 codes for AMR were only recently implemented and could be yet underused, leading to underestimation of its impact on hospital stays and associated costs of care.

Some other limitations could be addressed. We have only described hospital stays frequency and duration without differentiating hospital services (e.g., readmission to ICU) or medical subspecialty. In addition, we included RHC stays expenditure from data that are provided only for informational purposes. Thus, an uncertainty on the precise cost incurred by these hospitalizations could be raised, particularly for RHC-HOM and LTH pattern. Nevertheless, we believe having provided a general description that may be useful to both policy makers and practitioners.

In summary, our study documents the impact of AMR on post-discharge care trajectories, which is reflected in the consumption of care, particularly in terms of readmission for infection in acute care facilities and hospitalization at home. Our study should enable decision-makers to identify the most morbid and costly cases. Indeed bone, joint and device-associated infections and lower respiratory tract infections with AMR deserve the most attention, due to their significant societal cost, and require to be studied in greater depth in order to plan the most efficient actions possible. Furthermore, our results show, as expected, an over-representation of elderly patient, the most concerned population by AMR and particularly through healthcare-associated infections<sup>31</sup>, which highlights the need for patient care coordination between the different hospital actors and sectors.

Future studies are needed to evaluate more precisely the overall economic burden attributable to AMR.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.02.001.

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